REMARKS

In this Amendment, Applicant has cancelled Claim 6 without prejudice or disclaimer, amended Claims 1 – 5 and 7 – 12 and added Claims 13 – 14 to specify different embodiments of the present invention and overcome the rejection. It is respectfully submitted that no new matter has been introduced by the amended and added claims. All claims are now present for examination and favorable reconsideration is respectfully requested in view of the preceding amendments and the following comments.

REJECTIONS UNDER 35 U.S.C. § 101:

Claim 2 has been rejected under 35 U.S.C. § 101 as allegedly failing to define a patentable subject matter.

It is respectfully submitted that in view of the currently presented amendments, the rejection has been overcome. More specifically, Claim 2 has been amended to a method claim including specific and positive step(s).

Therefore, the rejection under 35 U.S.C. § 101 has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 101 is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112 SECOND PARAGRAPH:

Claims 1 – 12 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is respectfully submitted that Claims 1 – 5 and 7 – 12 have been amended to clearly point out and define the embodiment of the present invention. More specifically, the various informalities pointed out by the Examiner has been corrected.

Therefore, the rejection under 35 U.S.C. § 112, second paragraph, has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103:

Claims 1 – 12 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over WO/2000/044361 ('361) in view of Jatoi et al in further view of Casper, RC. Claims 1 – 12 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over WO/2000/044361 ('361) in view of US 2002/0099020 ('020).

Applicant traverses the rejection and respectfully submits that the embodiments of present-claimed invention as amended are not obvious over the cited references. At first, Claim 1 has been amended to define features that are significantly different from the cited references. According to MPEP 2143.03, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

'020 does not disclose the use of highly pure EPA in the treatment of anorexia nervosa (AN). On the contrary the document proposes the use of a variety of different omega-3 fatty acids, of no specific purity, ideally in combination with branched chain amino acids and antioxidants. The Casper paper talks about the fact that although the eating disorders are classified as psychiatric disorders there is no consensus about the nature of the underlying psychopathology. Casper also talks about the misnomer in that anorexia per se means loss of appetite and that is what is being talked about in the cancer patient of the Jatoi paper whereas anorexia nervosa is something different. Statements about "anorexia" or "weight loss" in general may not be directly teaching the treatment of AN.

Jatoi on pages 501-2 discloses the use of fish oil supplements to treat cancer-associated anorexia. This fish oil is very different from the pure EPA (as demonstrated in the context of eg depression in Amarin's earlier case which is the other main prior art). Disease-associated anorexia is again different from AN - and by way of example Applicant has attached a paper and which mentions on page 70 in the introduction that

they are discussing anorexia occurring as a specific syndrome during acute and chronic disease but that Anorexia Nervosa is a specific syndrome within eating disorders and they do not discuss this. Applicant respectfully questions the extent to which the work referred to in Jatoi - which is studying the treatment of cancer patients with the fish oils is relevant to the treatment of AN. Casper on page 97 discusses in the passage bridging columns 1 and 2 that the "anorexia" in AN is a misnomer. He draws distinctions between depressives and AN sufferers. There are AN patients who are not depressed.

On page 99 'TREATMENT STUDIES', Casper mentions the disappointments in using antidepressants to treat AN, despite an 'expectation of benefit'. In his CONCLUSIONS on page 101 he talks about depression triggering AN and the two becoming intertwined, but the evidence teaches against a common abnormality. Applicant does not see clear teaching from the art therefore that the highly pure EPA of the earlier Amarin case would obviously give success in treating AN.

It is respectfully submitted that there is much uncertainty about the link between AN and eg depression. The Examiner may have found one paper but there are others to say the opposite - for example the attached which shows that conventional anti-depressants don't work - or the Casper paper cited by the Examiner. Pages 2-3 of the present description conclude that 'there is no reason to believe on the basis of the prior art that AN might respond to EPA'. In contrast, the examples in the present description show significant changes in the patients taking EPA (95% pure - see example 2 on page 9 lines 4-5).

The inventors of the present application recognized that AN is a disorder in its own right, brought by physiological imbalances within a subject. They are not psychiatric disorders. In light of this recognition, the inventors were able to provide a novel and inventive solution to the problem of finding a non-expensive, easy to administer medication that acts directly on the physiological factors that cause AN.

As the experimental data provided in the specification shows, the purity of the EPA is an essential feature of the present invention. '020 makes no reference to the purity

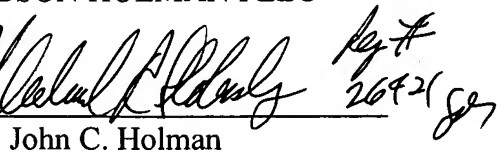
of any of the omega-fatty acids disclosed therein. The lack of any direct link between psychiatric and eating disorders is highlighted in documents D3 to D6 of the International Search Report. These papers consider similarities between the symptoms of eating disorders, such as AN and psychiatric disorders, such as depression and anxiety, but none of them research a clear conclusion over whether there is a physiological link between the two types of disorders. Even today, published papers fails to show a clear link between psychiatric disorders and eating disorders. We again refer the Examiner to the attached paper by Claudino A et al. (Treasure J. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004365) and in particular to the Author's conclusion on page 16 of the paper. Despite comparing a number of studies into the effect of various antidepressions on patients suffering from AN, the authors could "not find evidence of efficacy of antidepressants in the acute phase of AN".

Therefore, the rejection under 35 U.S.C. § 103 has been overcome. Accordingly, withdrawal of the rejections under 35 U.S.C. § 103 is respectfully requested.

Having overcome all outstanding grounds of rejection, the application is now in condition for allowance, and prompt action toward that end is respectfully solicited.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 
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Enclosures:

Claudino A et al. (Cochrane Database Syst Rev. 2006 Jan 5;(1):CD004365); and
Plata-Salaman, Anorexia During Acute and Chronic Disease, The Int'l J. of Applied & Basic Nutritional Science, Vol. 12, No. 2, pp. 69-78.

[Review]

Antidepressants for anorexia nervosa

AM Claudino, P Hay, MS Lima, J Bacaltchuk, U Schmidt, J Treasure

The Cochrane Database of Systematic Reviews 2006 Issue 1 (Status: *New*)

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Next

Abstract

Background
Anorexia Nervosa (AN) is an illness characterised by extreme concern about body weight and shape, severe self-imposed weight loss, and endocrine dysfunction. In spite of its high mortality, morbidity and chronicity, there are few intervention studies on the subject.

Objectives
The aim of this review was to evaluate the efficacy and acceptability of antidepressant drugs in the treatment of acute AN.

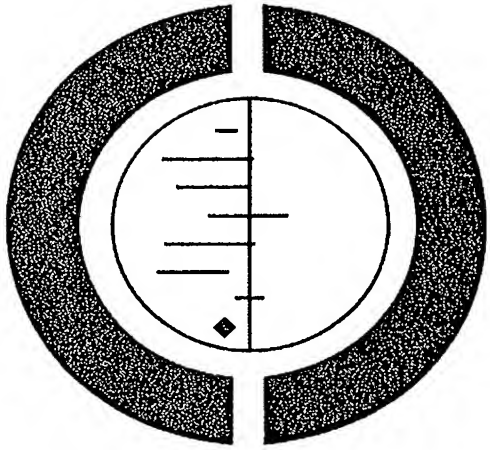
Search strategy
The strategy comprised of database searches of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, MEDLINE (1966 to April 28th, 2005), EMBASE (1980 to week 36, 2004), PsycINFO (1969 to August week 5, 2004), handsearching the International Journal of Eating Disorders and searching the reference lists of all papers selected. Personal letters were sent to researchers in the field requesting information on unpublished or in-progress trials.

Selection criteria
All randomised controlled trials of antidepressant treatment for AN patients, as defined by the Diagnostic and Statistical Manual, fourth edition (DSM-IV) or similar international criteria, were selected.

Data collection and analysis
Quality ratings were made giving consideration to the strong relationship between allocation concealment and potential for bias in the results; studies meeting criteria A and B were included. Trials were excluded if non-

Antidepressants for anorexia nervosa (Review)

Claudino AM, Hay P, Lima MS, Bacaltchuk J, Schmidt U, Treasure J



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Antidepressants for anorexia nervosa (Review)

Claudino AM, Hay P, Lima MS, Bacaltchuk J, Schmidt U, Treasure J

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Claudino AM, Hay P, Lima MS, Bacaltchuk J, Schmidt U, Treasure J. Antidepressants for anorexia nervosa. *The Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD004365.pub2. DOI: 10.1002/14651858.CD004365.pub2.

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Date of most recent substantive amendment: 04 November 2005

ABSTRACT

Background
Anorexia Nervosa (AN) is an illness characterised by extreme concern about body weight and shape, severe self-imposed weight loss, and endocrine dysfunction. In spite of its high mortality, morbidity and chronicity, there are few intervention studies on the subject.

Objectives
The aim of this review was to evaluate the efficacy and acceptability of antidepressant drugs in the treatment of acute AN.

Search strategy
The strategy comprised of database searches of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, MEDLINE (1966 to April 28th, 2005), EMBASE (1980 to week 36, 2004), PsycINFO (1969 to August week 5, 2004), handsearching the International Journal of Eating Disorders and searching the reference lists of all papers selected. Personal letters were sent to researchers in the field requesting information on unpublished or in-progress trials.

Selection criteria
All randomised controlled trials of antidepressant treatment for AN patients, as defined by the Diagnostic and Statistical Manual, fourth edition (DSM-IV) or similar international criteria, were selected.

Data collection and analysis
Quality ratings were made giving consideration to the strong relationship between allocation concealment and potential for bias in the results; studies meeting criteria A and B were included. Trials were excluded if non-completion rates were above 50%. The standardised mean difference and relative risk were used for continuous data and dichotomous data comparisons, respectively. Whenever possible, analyses were performed according to intention-to-treat principles. Heterogeneity was tested with the I-squared statistic. Weight change was the primary outcome. Secondary outcomes were severity of eating disorder, depression and anxiety symptoms, and global clinical state. Acceptability of treatment was evaluated by considering non-completion rates.

Main results
Only seven studies were included. Major methodological limitations such as small trial size and large confidence intervals decreased the power of the studies to detect differences between treatments, and meta-analysis of data was not possible for the majority of outcomes. Four placebo-controlled trials did not find evidence that antidepressants improved weight gain, eating disorder or associated psychopathology. Isolated findings, favouring amineptine and nortriptyline, emerged from the antidepressant versus antidepressant comparisons, but cannot be conceived as evidence of efficacy of a specific drug or class of antidepressant in light of the findings from the placebo comparisons. Non-completion rates were similar between the compared groups.

Authors' conclusions
A lack of quality information precludes us from drawing definite conclusions or recommendations on the use of antidepressants in acute AN. Future studies testing safer and more tolerable antidepressants in larger, well designed trials are needed to provide guidance for clinical practice.

PLAIN LANGUAGE SUMMARY

Anorexia nervosa (AN) is an illness of high mortality and chronicity. There is currently no leading treatment for anorexia nervosa and multiple interventions are often used. Pharmacotherapy is sometimes used as an adjunct to other treatment.

The aim of the present review was to evaluate the evidence from randomised controlled trials for the efficacy and acceptability of antidepressant treatment in acute AN. Seven small studies were identified; four placebo-controlled trials did not find evidence of efficacy of antidepressants in improving weight gain, eating disorder or associated symptoms, as well as differences in completion rates. Meta-analysis of data was not possible for most outcomes. However, major methodological limitations of these studies (e.g. insufficient power to detect differences) prevent from drawing definite conclusions or recommendations for antidepressant use in acute AN. Further studies testing safer antidepressants in larger and well designed trials are needed to guide clinical practice.

BACKGROUND

Anorexia nervosa (AN) is an illness characterised by extreme concern about body weight, with serious disturbances in eating behaviour leading to a self-imposed starvation state with severe weight loss. The current psychiatric classification manuals, Diagnostic and Statistical Manual, fourth edition (DSM-IV-TR) (APA 2000) and International Classification of Diseases, revision 10 (ICD-10) (WHO 1992), have based their criteria for AN diagnosis on the following aspects: (a) refusal to maintain weight within the normal range for height and age; (b) fear of weight gain; (c) body image disturbance and (d) absence of menstrual cycles or amenorrhoea in women (and loss of sexual interest in men). Body image becomes the predominant measure of self-worth, with concomitant denial of the seriousness of the illness. In DSM-IV-TR, two types of AN are described: the restricting type (in which the main feature is severe restriction of food intake and often excessive exercise), and the binge-purge type (in which patients regularly eat large amounts of food in a short period of time and/or engage in compensatory behaviours such as vomiting). As well as the impact on psychological wellbeing, AN has notable and sometimes fatal medical consequences from the effects of starvation and purging behaviours. In particular, growth and development are often delayed when AN occurs in childhood or early adolescence (Wiseman 1998).

Although AN is not a common condition in the population as a whole, its morbidity and mortality are amongst the highest of all functional psychiatric disorders due to malnutrition, purging behaviour and suicide. In outcome reviews, a mean crude mortality rate of 5% (Steinhausen 2002; Sullivan 1995) and standardised mortality rates between 1.36% and 17.80% (indicating a slight to an almost 18-fold increase in mortality in patients with AN) have been reported (Nielsen 1998). AN affects mainly adolescent girls and young women and is up to ten times more common in women than in men. It has a point prevalence of no more than 0.5% within this group (Aalto-Setala 2001; Verhulst 1997). A systematic review of 12 cumulative incidence studies reported an estimated mean yearly incidence in the general population of 18.5/100.000 (standard deviation (SD) = 21.01) in women and 2.25/100.000 (SD = 2.63) in men (Pawluck 1998). Increases in incidence of AN in young women over the second half of the 20th century have been reported (Lucas 1991; Pawluck 1998).

The aetiology of AN is thought to be multi-factorial (Jacobi 2004; Schmidt 2003; Collier 2004) and involves environmental factors (social and cultural factors), psychological and developmental aspects, and biological/genetic vulnerabilities. As yet it is not known how these factors interact in the development of eating disorders. Great emphasis has been given to sociocultural explanations in the last decades, such as pressure to be slim, with slenderness as a measure of beauty (Stice 2002), and modernisation processes in cultures in transition associated with confused gender roles and identities (Nasser 2000). The advent of new biotechnologies (neuroimaging, molecular biology) has led to a growing interest in putative biological components of the aetiology of eating disorders (Schmidt 2003), especially to the genetic contribution (Bulik 2000; Wade 2000).

It is known that AN and bulimia nervosa (BN) cluster in families. One controlled family study found that female relatives of probands with AN or BN had, respectively, approximately eleven-fold and twelve-fold greater lifetime risks of full syndrome AN than relatives of unaffected controls (Strober 2000), suggesting a common or shared familial diathesis for eating disorders. Population-based twin studies have estimated mean heritabilities for a broad anorexia-like phenotype of 58% to 74% (Wade 2000; Klump 2001; Kortegaard 2001). The low prevalence of the disorder, low sample sizes and many common methodological problems of the studies make it hard to produce more precise estimates of genetic effects in the aetiology of AN.

The findings of common association (comorbidity) of eating disorders and certain psychiatric symptoms and disorders have led to the hypothesis that a predisposition to a particular personality type, to affective, anxiety or obsessive-compulsive disorder (OCD), or a physiological vulnerability may all play a role in the genetic contribution to the aetiology of AN (Klump 2001). Family and twin studies have found that there are shared as well as unique genetic influences on major depression and AN (Wade 2000; Strober 2000). In one controlled family study (Lilenfeld 1998) there was an in-

creased risk of obsessive-compulsive personality disorder (OCPD) in relatives of AN probands and the rate of OCPD was similar in the relatives, whether or not the person with anorexia nervosa was comorbid for OCPD. This suggests linked transmission for AN and OCPD.

From the developmental perspective, features that precede the onset of the eating disorder and are present in childhood, such as traits reflecting obsessive-compulsive personality (perfectionism, rigidity, harm-avoidance, obsession with symmetry, negative affect and over-control), can act as risk factors for developing eating disorders and represent markers for a broader phenotype of a subgroup of AN patients possibly associated with serotonergic dysfunction (PRCG 2001; Anderluh 2003; Connan 2003a; Steiger 2004). One recent systematic review classified risk factors for both anorexia nervosa and bulimia nervosa according to their potency and specificity (Jacobi 2004). The only two high potency risk factors for AN were being female and exercising before onset. Feeding difficulties, gastrointestinal problems, problems with sleeping and over involved parenting were medium potency risk factors for AN, as were childhood perfectionism, obsessive-compulsive personality disorder and negative evaluation of self. Preterm birth, perinatal complications and birth trauma were specific risk factors for AN, as were OCD, perfectionism and negative self-evaluation.

An increasing number of molecular genetics studies in eating disorders have focused on candidate genes that could be involved in neurotransmitter pathways regulating behaviour or implicated in the control of weight, feeding and energy expenditure (Gorwood 1998). Studies have targeted mainly serotonin-linked genes (Collier 1997; Enoch 1998; Kaye 2001a; Devlin 2002) based on the involvement of the serotonin system in the control of appetite and satiety, and its possible association with some of the personality traits underlying restricting-type AN. Other genes, such as the brain-derived neurotrophic factor gene have also been studied and found to be associated with susceptibility to eating disorders, possibly through its involvement in affective symptoms (Ribases 2004).

With regard to the neurobiological contribution to the development of eating disorders, many questions remain unanswered. A number of abnormalities in neurotransmitters (serotonin, dopamine, norepinephrine), neuropeptides and neuroendocrine hormones have been described in AN during the acute phase of the illness (Kaye 1998; Connan 2003b), most of them considered to be changes due to the starvation state and to the pathological eating behaviours (Gendall 1999; Mantzoros 1997; Connan 2003b), but others also seeming to persist after weight restoration (Kaye 1998; Kaye 1999a). Perceptions of hunger and satiety seem to reflect the complex integration of cognitive sets and internal physiology. Energy intake is clearly reduced in AN, but it is controversial whether appetite is affected: a tight cognitive control of normal appetite has been suggested for some (Palmer 2000) while others consider appetite to be impaired (Pinel 2000). Research on changes in neurotransmitter systems is of considerable interest, not only because of their potential role in the pathophysiology of eating disorders, but for improving pharmacological approaches in the treatment of these disorders. Brain neurotransmitters play an important role in the modulation of appetite behaviours, post-prandial satiety, neuroendocrine function, mood and many behaviours associated with AN. Attempts have been made to identify putative predisposing factors that either pre-date the weight loss or that may have a predisposition to recurrence or maintenance of low-weight. Functional activity of central serotonin systems has been found to be diminished during low-weight, but may be abnormally increased in long-term weight-recovered AN patients (Kaye 1991a; Kaye 1998), leading to the hypothesis that some individuals who develop AN possibly had high levels of serotonin activity "before the onset of the illness", i.e. a brain serotonergic dysfunction that might contribute to the pathophysiology of AN. However, it cannot be ruled out that decreased levels of cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) in acute AN patients are related to reduced intake of tryptophan and increased levels of CSF 5-HIAA are a physiological consequence of chronic malnutrition (de Zwann 2003b). Additional findings of reduced noradrenergic and dopaminergic activity have been described in ill AN patients (Kaye 1984; Pirke 1996) with persistent low levels of CSF homovanillic acid (HVA) reported in the subgroup of restricting-type AN after recovery and also hypothesised as another trait-related vulnerability related to altered reward, novelty seeking and motor activity (Kaye 1999a).

Moreover, enhanced satiety has been proposed to be associated with elevated cholecystokinin (CCK) release in AN, and tends to normalise with weight gain, but can be reduced by the serotonergic dysfunction (Stallone 1989). Mantzoros 1997 found leptin levels to be lowered in acute AN, but the CSF to plasma ratio was higher in patients compared to controls; at post-treatment, however, both leptin levels normalised even before weight was fully restored, possibly "contributing to resistance to weight gain and to incomplete weight recovery", according to the authors. Additional findings of altered response of cortisol and insulin to a meal following recovery may represent sequelae of AN or a vulnerability factor for the disorder. Hypothalamic function seems to be more implicated in the appetite imbalance than peripheral signals of energy homeostasis, with an aberrant response to chronic stress (demonstrated by persistent elevated corticotropin-releasing hormone (CRH)) being a possible pathophysiological factor in AN (Connan 2003b).

Structural neuroimaging studies in AN have also reported alterations, such as increased cerebrospinal fluid and ventricles, and decreased brain tissue, most of which are apparently linked to endocrine and metabolic consequences of starvation and are reversible with weight restoration (Katzman 2003; de Zwann 2003b). However, some recent evidence that emerged from functional neuroimaging studies in patients with early-onset AN raised the possibility of a predisposing biological substrate involved in

the pathogenesis of AN for some patients. Results from these studies suggest temporal lobe abnormality (Gordon 1997; Lask 2005) and limbic system dysfunction (Chowdhury 2003; Lask 2005). Lask 2005 found that unilateral reduction of blood flow in the temporal region was associated with impaired cognitive function, such as impaired visuospatial ability, impaired visual memory and enhanced information processing. The authors considered that the "hypoperfusion could be a primary phenomenon or a result of starvation that either reversed slowly or was irreversible".

Treatment goals in AN include stabilisation of medical and nutritional status (restoration of weight and normal menstrual cycles), re-establishment of healthy patterns of eating (including cessation of restriction and purging), improvement of body image and amelioration of the morbid pre-occupation with weight and shape. Non-specific aims of the treatment include improvement in functioning and quality of life. The treatment of AN is frequently long-term and challenging. Prognostic studies have shown that AN is often a chronic illness, with only half of the patients achieving full recovery in long-term follow-up studies (Hsu 1986; Steinhausen 2002). Currently, recommended treatments for AN rely on a multidisciplinary approach, due to the multidimensional nature of the illness (APA 2000; NCCMH 2004), but there is limited empirical support for the range of treatments used (Fairburn 2005; Agras 2004). Patients can be treated in an inpatient or outpatient/day care setting depending on their clinical and psychiatric condition. Because of the severe and potentially irreversible effects of starvation, restoration of weight is considered an important initial treatment focus. Combinations of individual and family psychotherapies, nutritional rehabilitation and pharmacotherapy are usual.

The rationale for pharmacological treatment of AN is based on neurobiological research into the control of appetite and food intake, and on biological models of AN as discussed earlier (Connan 2003b; de Zwann 2003b; Kaye 1991a) on clinical observations and uncontrolled studies (De Zwann 2003a). Pharmacotherapy is a frequent adjunctive intervention. Different classes of drugs (e.g. neuroleptic medication or cyproheptadine, a weight-inducing drug) have been tried with the aim of reducing the core symptoms of AN and associated psychopathology (Bosanac 2005), or to stimulate appetite (Halmi 1986), but there is little current evidence of their efficacy or effectiveness (Treasure 2004). For that reason, recent mental health guidelines (APA 2000; NCCMH 2004) do not recommend medications as first-line treatment for AN.

Antidepressants are the first-line agents for treatment of depression, obsessive-compulsive disorder and bulimia nervosa (Geddes 2002; Soomro 2002; Fineberg 2004; Bacaltchuk 2005). Researchers have attempted to link these disorders to eating disorders based on their common underlying neurobiological abnormalities in catecholamine metabolism, especially the serotonergic dysfunction (Jimerson 1990; Kaye 1991a; Chamberlain 2005), on findings of frequent comorbidity (Braun 1994), their shared genetic risk and personality traits (Lilenfeld 1998; Wade 2000; Strober 2000; Anderluh 2003; Steiger 2004; Graybiel 2005). Additionally, many patients with AN also suffer from symptoms that are commonly targeted with antidepressants, such as depressive symptoms (e.g. low mood, loss of interest, social isolation) and obsessive-compulsive symptoms (related to eating/food and other behaviour) (Mayer 1998). Finally, antidepressant drugs have also been considered of interest in the treatment of AN due to their weight gain inducing properties (as a side effect), especially the tricyclics (Fernstrom 1995).

De Zwann 2003a reviewed studies on drug treatment of AN and found some evidence from uncontrolled studies that antidepressants could help in weight gain (Gwirtsman 1990; Pallanti 1997; Frank 2001a). They noted, however, that confounding variables (e.g. other adjunctive treatments) limited the confidence in the findings. Non-randomised trials comparing selective serotonin reuptake inhibitor (SSRI) treatment (combined to other interventions) to no drug treatment report mixed results (Strober 1999; Ferguson 1999; Santonastaso 2001; Ruggiero 2003). For example, Ruggiero 2003 found a significantly higher weight gain in AN outpatients treated with nutritional management and fluoxetine compared to patients treated only with nutritional management. In contrast, Strober 1999 did not find any advantage of adding fluoxetine to inpatient treatment in terms of weight gain or AN symptoms compared to matched historical controls, who received the same interventions without adjunctive pharmacotherapy. Randomised controlled trials testing antidepressant drugs are considered a better level of evidence in treatment studies, but unfortunately are scarce in AN (Treasure 2004).

The aim of this systematic review was to evaluate the efficacy and acceptability of antidepressant drugs for the treatment of acute AN. Data from several studies in meta-analysis might help increase the knowledge of the effects of these drugs.

OBJECTIVES

The primary objective of this review was to determine the clinical efficacy and acceptability of antidepressants when compared to placebo in patients with anorexia nervosa (acute phase).

Secondary objectives were:
(i) to investigate the efficacy and acceptability of different classes of antidepressant drugs;
(ii) to evaluate the efficacy of antidepressants with respect to general psychiatric symptoms usually associated with anorexia nervosa and global clinical improvement.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients diagnosed with anorexia nervosa by any criteria such as Russell's, ICD-9 or ICD-10, DSM-III, DSM-III-R or DSM-IV (including both subtypes) or by "clinical judgement", independent of gender or age.

Types of intervention

RCTs lasting at least four weeks and comparing any antidepressant drug to:
(i) placebo;
(ii) other antidepressant drug.

Treatment could be conducted on an out or inpatient basis (primary, secondary or tertiary sectors), as monotherapy, or as adjunctive therapy to other non-pharmacological treatment.

Types of outcome measures

Primary outcome measures

1. Efficacy at the end of treatment, measured through weight gain or weight restoration as follows:

(a) end-of-treatment mean absolute weight or body mass index (BMI) (where groups were not significantly different in mean weight/BMI at start of treatment);
(b) number of patients achieving target weight or weight within a normal range (e.g. BMI >18 or weight >85% of average for age, gender and height; data were entered in tables as number or patients not achieving target weight);
(c) mean rate of weight gain;
(d) number of days to achieve ideal weight;
(e) any other consistent measure of change in weight.

Secondary outcome measures

1. Efficacy at the end of treatment, through the following outcome measures:

(a) eating disorder symptoms: measured by mean scores on any recognised and validated eating disorder questionnaire or interview e.g. Eating Attitudes Test (EAT), Eating Disorders Inventory (EDI), Bulimic Investigatory Test Edinburgh (BITE), Yale-Brown-Cornell Eating Disorder Scale (Y-Brown-Cornell EDS);
(b) recovery evaluated through scales such as:
(i) Morgan and Russell (Morgan 1975) narrow criteria of:

1. good outcome, namely normal body weight (>85% of average for age, gender and height) with normal menstruation
2. intermediate outcome, namely normal body weight (>85% of average for age, gender and height) with no menstruation
3. poor outcome, neither obtaining normal menses or weight

(ii) Morgan and Russell (Morgan 1988) broader criteria for average outcome;
(c) level of depression symptoms: as measured by mean scores on any recognised and validated depressive rating scale e.g. Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Schedule for Affective Disorders and Schizophrenia - Change (SADS -C);
(d) level of anxiety symptoms (including obsessive-compulsive ones): as measured by mean scores on any recognised and validated obsessive-compulsive rating scale e.g. Hamilton Depression Anxiety Scale (HDAS), Hopkins Symptom Checklist (HSCL), Yale-Brown Obsessive Compulsive Scale (Y-BOCS);
(e) clinical improvement: as measured by any scale (e.g. Clinical Global Impression (CGI) - score of "much improved" or "improved" (dichotomous) or mean scores; Global Severity Scale and Global Improvement Scale ratings - categories of improvement (dichotomous).

2. Acceptability of the treatment measured by:

(a) proportion of non-completers (drop-outs) due to any reason or post-randomisation exclusions;
(b) proportion of non-completers due to adverse effects;
(c) number of subjects reporting side effects.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Depression, Anxiety and Neurosis Group methods used in reviews.

Electronic searches:

The Cochrane Depression, Anxiety and Neurosis Review Group Register (CCDANCTR-Studies) were searched using the following terms:
Diagnosis = "Anorexia Nervosa" or "Eating Disorders"
and
Intervention = "Antidepressive Agents" or "Monoamine Oxidase Inhibitors" or "Selective Serotonin Reuptake Inhibitors" or "Tricyclic Drugs" or Acetylcarnitine or Alaproclate or Amersergide or Amiflamine or Amineptine or Amisulpride or Amitriptyline or Amoxapine or Befloxatone or Benactyzine or Brofaromine or Bupropion or Butriptyline or Caroxazone or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or Clorgyline or Clorimipramine or Clovoxamine or Deanol or Demexiptiline or Deprenyl or Desipramine or Dibenzipin or Diclofensine or Dothiepin or Doxepin or Duloxetine or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluparoxan or Fluvoxamine or Idazoxan or Imipramine or Iprindole or Iproniazid or isocarboxazid or Litoxetine or Lofepramine or Maprotiline or Medifoxamine or Melitracen or Metapramine or Mianserin or

Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nomifensine or Nortriptyline or Noxiptiline or Opipramol or Oxaflozane or Oxaprotiline or Pargyline or Paroxetine or Phenelzine or Piribedil or Pirlindole or Pivagabine or Prosulpride or Protriptyline or Quinupramine or Reboxetine or Rolipram or Sertraline or Setiptiline or Sulpiride or Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tianeptine or Toloxatone or Tomoxetine or Tranylcypromine or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Viqualine or Zimeldine

In order to test the sensitivity of the CCDAN database, searches were also performed in the following databases, using the standard search phrase for controlled clinical trials (Dickersin 1994), associated to the previous anorexia and antidepressants phrases: MEDLINE (1966 to April 28th, 2005), EMBASE (1980 to week 36, 2004), PsycINFO (1969 to August week 5, 2004).

Social Sciences and the Science Citation Index were searched for all selected papers.

The searches were conducted with the assistance of the Depression, Anxiety and Neurosis Cochrane Group.

Handsearches:
The International Journal of Eating Disorders since its first issue. The reference lists of relevant articles and book chapters on treatment or pharmacological treatment of AN were searched.

Personal communication:
Personal letters to experts in the area of anorexia nervosa treatment in the US, UK, Europe, NZ and Australia were sent requesting information for unpublished or ongoing trials.

METHODS OF THE REVIEW

Selection of trials

The first author (AMC) selected the articles that met criteria for this systematic review by scrutinising abstracts of all the papers that came out of the searches and that met the criteria for inclusion.

Quality assessment

Two reviewers (AMC and JB) independently assessed the methodological quality of the included studies giving consideration to the strong relationship between quality of allocation concealment and potential for bias in the results, using the following criteria (based on the guidelines proposed by Mulrow 1999):

A. Low risk of bias (adequate allocation concealment): i.e. patients were randomised by researchers who were not responsible for recruiting participants, and precautions were taken to prevent manipulation of randomisation codes (for example using numbered or coded bottles and serially numbered, sealed, opaque envelopes).
B. Moderate risk of bias (some doubt about the results): i.e. when trials do not report any concealment approach, but state that patients were randomly allocated.
C. High risk of bias (inadequate allocation concealment): i.e. inadequate approaches to concealment allocation, such as alternation, reference to case record numbers, dates of birth, day of the week or any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers.

Trials were included if they met criteria A or B.

Because of the rarity of trials in this area and methodological problems associated with conducting trials in AN, trials were only excluded if the non-completion rates were >50%.

A further quality assessment was also performed using the 23 item criteria from the Cochrane Collaboration Depression, Anxiety and Neurosis Group Quality Rating Scale (QRS) (Moncrieff 2001). The QRS consists of 23 items, including items on sample size, allocation, use of diagnostic criteria, compliance, attrition and statistical analysis. Total scores can range from 0-46. Exclusions of trials were not made based on these criteria.

In addition, a criterion evaluating "information on baseline nutritional status" was also evaluated as this was considered an important issue for this review.

Data extraction

Two reviewers (AMC, JB) independently extracted the data using a standardised data extraction sheet in order to ensure reliability. Any disagreement was discussed and the decisions documented. Authorship was not concealed at the point of data collection.

First authors of the studies were contacted through letters and emails to ask for information about the methodology used (for quality evaluation) or results that were not available in the published trial(s). In cases where there was no reply after four weeks, only published data were considered. All additional information obtained were included in the review. Data from unpublished trials were not included.

Analysis

Data were entered into Review Manager (RevMan) 4.2.6 software for analysis.

1. Dichotomous data:
Relative risk (RR) analyses were conducted for dichotomous outcome data (RR was preferred to the odds ratio as it is a more conservative statistic and appropriate where the outcome is not a rare event). Whenever possible, analyses were performed according to intention-to-treat (ITT) principles (e.g. number of improved patients out of the number of patients randomised to experimental and control groups). If no information was available (either from the report or from the authors) for dichotomous missing data, assumptions were made based on the worst result for the outcome (a negative outcome), such as "patient did not achieve target weight or weight within normal range", "drop-out was due to side-effects or treatment failure".

2. Continuous data:

Standardised mean difference (SMD) analyses were conducted for continuous outcome data. The SMD was chosen as different scales are often used to assess psychopathology. Continuous data were analysed as provided by authors in original studies, i.e. endpoint scores for groups or change in scores from baseline to endpoint. The method adopted by authors for analysing continuous outcomes was described when provided (for instance, last observation carried forward (LOCF)), as they could vary and have implications for the assessment of the results. Data on the number of patients evaluated for each variable at the end of treatment were presented when available.

95% confidence intervals (CI) were reported for both dichotomous (RR) and continuous (SMD) variables, based on the random effects model (DerSimonian 1986), as this takes into account any differences between studies even if heterogeneity is not statistically significant.

3. Heterogeneity:
I-squared tests (I^2) for homogeneity were done. I^2 test describes the percentage of total variation across studies that is due to heterogeneity rather than chance alone, and a value greater than 50% is considered substantial heterogeneity (Higgins 2003). If significant heterogeneity was found (through graphical inspection or by I^2 tests), trials contributing most to heterogeneity were removed in sensitivity analyses and reasons for heterogeneity discussed.

4. Sensitivity analyses:
Sensitivity analyses were planned as follows:
(i) where diagnosis of AN was not defined according to rigorous criteria (DSM, ICD) but through other forms of evaluation (e.g. described as "clinical");
(ii) if completion rates of less than 70% were obtained in any arm of the trial (post hoc sub-group analysis);
(iii) to test if assumptions made from reviewers based on "intention to treat principles" caused any substantial change in results;
(iv) if heterogeneity among studies was found (to verify which trials were contributing most to heterogeneity).

5. Addressing publication bias:
Wherever the number of trials allowed, funnel plots were planned to be done to assess the possibility of publication bias.

6. Subgroup analyses:
Two subgroup analyses were planned to compare:

(i) efficacy across different classes of antidepressants;
(ii) efficacy across setting of treatment (in or outpatient treatment).

DESCRIPTION OF STUDIES

1. Search

A total of 1303 citations, including papers and abstracts, on antidepressants for patients with anorexia nervosa or eating disorders were identified from the searches (based on strategies described in the Search Strategy section):

211 from MEDLINE (1966 until April 28, 2005)
593 from EMBASE (1980 until end of week 36, 2004)
175 from psycINFO (1969 until end of August, 2004)
04 from the International Journal of Eating Disorders (from the first issue up to March 2005 issue)
18 from CCDANCTR (until Feb 14, 2005)
302 from SOCIAL SCIENCES (from 1956 to April 28th 2005) and SCIENCE CITATION INDEX (from 1945 to April 28th 2005) of articles included in the review.

One hundred and sixty four citations were selected for examination of abstracts. From these, 40 studies were fully examined. Seven trials fulfilled the inclusion criteria and 33 studies were excluded (see table of excluded studies for details). No ongoing or unpublished RCT related to the objectives of this review was identified in searches in Current Contents database or from experts in the field.

Funnel plots to verify possible publication biases were not conducted as the paucity of trials did not allow this.

2. Excluded studies

Studies excluded from the searches were mainly review articles on pharmacological treatment of eating disorders, trials of treatment of other eating disorders, bulimia nervosa and binge-eating disorder, or drug trials of other psychiatric disorders (e.g. depression).

Within the selected articles (number (N) = 40), seven studies fulfilled inclusion criteria and 33 studies did not (see table of excluded studies for details). Thirteen of the excluded studies were RCTs:
three tested other drug classes (zinc, lithium carbohidrate, pimozide) in AN;
one tested additional nutritional supplements to fluoxetine in AN;
three evaluated aspects in AN patients receiving antidepressant treatment that were not pertinent to the questions of this review;
one tested a non-pharmacological intervention for AN;
one tested citalopram versus a no-drug control group in AN;
two (Halmi 1982; Halmi 1983) were partial data of one of the included studies (Halmi 1986), and
two were relapse prevention studies in AN.

The remaining excluded studies were not randomised trials (N = 20):
one study was a quasi-randomised comparison of venlafaxine versus fluoxetine in atypical AN patients;
two were non-randomised, open controlled trials: one tested adjunct fluoxetine to nutritional management versus nutritional management only (control group) and the other tested adjunctive sertraline to cognitive behaviour therapy (CBT) and nutritional counselling versus CBT and nutritional counselling only (control group);
one was a non-randomised, open label trial of drug treatments (lithium, carbamazepine, antidepressants) in AN;

one was an open label trial of fluoxetine compared to a matched historic control group;
five were retrospective observational studies;
two studies evaluated relapse prevention in AN;
four were uncontrolled open trials in AN;
one was a single-case study of interaction of antidepressant to psychotherapy and
three were case reports of drug treatment in AN.

Comparisons of pharmacological therapy (including antidepressant drugs) with individual psychotherapy, or combination of pharmacological therapy and individual psychotherapy versus either drug therapy or psychotherapy alone have been included in another systematic review - "Individual psychotherapy in the outpatient treatment of adults with anorexia nervosa" (Hay 2003).

3. Included studies

Seven published studies were selected for inclusion in this review: four of them compared antidepressants to placebo (Lacey 1980; Biederman 1985; Halmi 1986; Attia 1998) and three compared antidepressant drugs (Brambilla 1995a; Brambilla 1995b; Ruggiero 2001).

One author replied to the letters and gave information concerning two studies (Brambilla 1995a; Brambilla 1995b). Two other authors also replied to the letters but did not have additional information over and above what was published in the articles (Halmi 1986; Biederman 1985).

Summary of the characteristics of the included studies

Size of the samples
The size of samples ranged from 16 to 48 patients in the placebo controlled trials and from 13 to 35 patients in the antidepressants comparisons trials. Halmi 1986 had the biggest sample of the studies included (23 drug arm by 25 placebo) and Brambilla 1995b the smallest group sizes (6 fluoxetine by 7 amineptine).

Setting
Most of the placebo controlled studies involved only inpatient treatment (three of four studies); one trial (Biederman 1985) involved mainly inpatients (20/25) and only five subjects were treated as outpatients. Of the comparisons between antidepressants, two RCTs studied outpatients (Brambilla 1995a; Brambilla 1995b) and the other was conducted with inpatients (Ruggiero 2001). Two of the RCTs were multi-centre studies (Biederman 1985; Halmi 1986).

Duration of trials
The planned duration of the trials ranged from five weeks (Biederman 1985) to four months (Brambilla 1995a; Brambilla 1995b). All studies (except Lacey 1980) did not have follow-up periods.

Participants
A total of 178 patients were randomised in total, 120 in the placebo controlled trials and 58 in the antidepressants comparisons' trials. All trials but one (Lacey 1980) used operational criteria for diagnosis (mainly DSM-III, DSM-IIIR or DSM-IV). Lacey 1980 did not provide criteria for diagnosis of AN but stated that patients were "admitted to anorectic unit at Atkinson's Morley Hospital". Three studies included both types of AN patients (Lacey 1980; Halmi 1986; Attia 1998), two included only restrictive type AN (Brambilla 1995a; Ruggiero 2001), one included only bulimic/purging type AN (Brambilla 1995b) and the last one did not specify type of AN (Biederman 1985). Two trials did not report gender and the rest involved only females. Patients were mainly young adults with mean ages between 20 and 30 years in six studies, and only one study presented a younger group of patients of mean age around 17 years (Biederman 1985). Duration of illness varied among studies with means that ranged from around two years to eight years in six studies (which provided that information), including patients with a duration of illness that as brief as three months or as long as 14 years.

Interventions
In all studies the drug was added to other kinds of interventions (psychotherapies, nutritional therapy), including intensive re-feeding programmes for hospitalised patients.

Low to modest doses of drugs were used in four trials (Lacey 1980; Biederman 1985; Halmi 1986; Ruggiero 2001) while the other studies used higher doses (e.g. fluoxetine 60mg in Attia 1998; Brambilla 1995a; Brambilla 1995b).

Outcomes
All studies provided data concerning the primary outcome weight gain (with varied types of measure) and all (except Lacey 1980) also evaluated eating disorders and/or general psychopathology.

Specific information concerning the main characteristics of each study is provided in the Table of Included Studies.

METHODOLOGICAL QUALITY

As there were so few trials, the levels of agreement on quality of trials and data extraction were not tested statistically. All data related to quality ratings and outcomes were extracted by two reviewers, who then reached consensus on final ratings.

The reviewers added the criteria "information on baseline nutritional status" to the CCDAN quality-criteria items, as this was considered an important issue for this review.

Randomisation
All studies were described as randomised but no details about the concealment of allocation were given in any of the articles. Thus there was uncertainty about whether allocation was adequately concealed; for that reason five studies were graded as "B" (Attia 1998; Halmi 1986; Biederman 1985; Lacey 1980; Ruggiero 2001). One author (Brambilla 1995a; Brambilla 1995b) answered queries and reported that randomisation codes were protected by

sealed opaque envelopes; these two studies were therefore graded as "A".

Blinding and test of integrity
All four placebo controlled studies were double-blind, but no study reported testing the integrity of blindness. One of the studies comparing different antidepressants (Ruggiero 2001) was single-blind (outcome assessor) but no test of the integrity was reported, and the two remaining trials in this group (Brambilla 1995a; Brambilla 1995b) were open label.

Objectives and main outcome
Three studies provided clear objectives (Attia 1998; Biederman 1985; Ruggiero 2001); three objectives were clear but the main outcomes were not specified a priori (Brambilla 1995a; Brambilla 1995b; Halmi 1986) and in one early study the objectives were unclear (Lacey 1980).

Sample size per group
All studies involved less than 50 patients per group. Indeed in all, fewer than 50 patients were randomised (considering only the arms used for comparisons of this review); thus overall sample sizes were small.

Planned duration of trial and follow-up
Four studies (Attia 1998; Biederman 1985; Halmi 1986; Ruggiero 2001) were planned to be of short duration (maximum three months), with no follow-up period. One trial did not report a planned duration (duration variable, maximum time not established), and its mean duration was around 10 weeks (Lacey 1980); nevertheless this is the only trial that presented follow-up data (partial) at one year and at four years. Brambilla's trials (Brambilla 1995a; Brambilla 1995b) had a moderate duration of four months.

Power calculation
The only trial that mentioned conducting a power calculation, albeit without giving details on this, was Attia 1998; all the others did not report a power calculation.

Description of treatment
All studies presented details of drug treatment and adjunctive treatments.

Source of subjects
Most studies described the source of subjects and representative samples were taken. Ruggiero 2001 excluded patients younger than 17 years old.

Diagnostic criteria
All trials used diagnostic criteria and/or inclusion criteria (mainly DSM-III, DSM-IIIR or DSM-IV) except for one trial (Lacey 1980) in which patients were "admissions to a specialist eating disorders unit" with no further information on the diagnostic criteria. Biederman 1985 included one patient who had a weight loss of 19% of the body weight (BMI not stated), less than asked for by DSM-III criterion of weight used in the trial, but all other criteria were fulfilled. In Attia's study (Attia 1998), three patients had irregular menses, but were included because they were substantially underweight. In one of Brambilla's studies (Brambilla 1995b) only three patients were amenorrheic and the rest had irregular menses or oligomenorrhoea. The absence of amenorrhoea could technically put these patients outside diagnostic criteria for anorexia nervosa, but the reviewers decided to accept and include these trials because amenorrhoea is considered a controversial diagnostic criteria in AN (Garfinkel 1996).

Exclusion criteria and number of exclusions and refusals
Only one study did not specify any exclusion criteria (Lacey 1980). Except for Biederman 1985, who reported the number of suitable patients who refused to participate (18 patients), only Ruggiero 2001 reported that patients were selected from a sample of 164 AN patients; this study presented data from 35 patients who finished the re-feeding programme but did not differentiate between eligible patients who refused to participate, the number of exclusions (due to meeting exclusion criteria) before randomisation, and the number of exclusions after randomisation (for the 129 patients excluded).

Description of sample demographics
Three studies (Biederman 1985; Lacey 1980; Halmi 1986) gave full details of sample demographics. The remaining studies gave little or basic information.

Assessment of compliance with experimental treatment
Only two trials assessed drug compliance by measuring plasma levels (Attia 1998; Biederman 1985; Brambilla 1995a; Brambilla 1995b) noted that in her study compliance with drug treatment was ensured through family support. None of the other trials made any reference to assessment of compliance.

Details on side-effects
Three studies provided information on side-effects per group (Attia 1998; Biederman 1985; Halmi 1986) but the details were inadequate (Halmi 1986). Two authors gave no details on side-effects (Lacey 1980; Ruggiero 2001) and (Brambilla 1995a; Brambilla 1995b) reported that there were no side-effects in her trials.

Description of completion rates
Three studies reported on withdrawals before the end of the trial both detailing and breaking down the reasons for this (Attia 1998; Halmi 1986; Lacey 1980); two did not refer to drop-outs but the data imply, and the present reviewers assumed, that there were no people lost at follow-up (Biederman 1985; Ruggiero 2001); the two remaining studies (Brambilla 1995a; Brambilla 1995b) did not report on drop-outs in the published data, and when the authors were contacted they informed us that there were no withdrawals.

Outcomes description and use of validated instruments
Outcomes were clearly described in four studies (Halmi 1986; Attia 1998; Brambilla 1995a; Brambilla 1995b). Lacey 1980; Biederman 1985 provided some outcomes in graphical form, from

which it was not possible to acquire raw data for synthesis. Most studies presented data from primary and secondary outcomes as continuous data, but some means were provided without standard deviations (Lacey 1980; Ruggiero 2001). Most studies used validated instruments (e.g. EAT, BITE, EDI, SCL90, HRS-D, HRS-A, BDI, SADS-C) to evaluate eating disorder symptoms and associated psychopathology. Evaluations that were not related to the scope of this review or that were not based on validated instruments were not considered (Lacey 1980; Halmi 1986; Ruggiero 2001). The only unvalidated scales considered in this review were scales of improvement in the global state (Attia 1998; Biederman 1985).

Information on baseline nutritional status

Information on baseline nutritional status was provided by three main measures in studies (for the whole sample or by group): BMI, percentage of ideal body weight or just weight. The mean BMI at baseline was reported in only three studies (Attia 1998; Brambilla 1995a; Brambilla 1995b) and ranged from 14.7 to 16.7 kg/m^2. Data on mean percentage of ideal body weight at baseline was given in three studies (Attia 1998; Biederman 1985; Halmi 1986) and ranged from 69.0% to 82.4% among studies.

Although it is not a good measure of "adequacy" of weight, mean baseline weight was provided in four studies (Attia 1998; Biederman 1985; Lacey 1980; Ruggiero 2001) and varied from 35.5 kg to 41.7 kg. These data suggest that overall patients were substantially underweight at baseline, but the level of severity of weight loss cannot be precisely compared between trials in light of the different measures provided.

Information on comparability of groups and adjustment for differences in analysis

All studies had comparable groups in weight or initial BMI, although this information was not always provided (Halmi 1986; Lacey 1980; Ruggiero 2001). Where provision of initial data allowed this, comparability of groups at baseline was tested by the reviewers. Four studies did not provide information on the comparability of groups in terms of their demographics or clinical histories (Brambilla 1995a; Brambilla 1995b; Halmi 1986; Ruggiero 2001); two studies reported on comparability of their study groups in all variables (Biederman 1985; Lacey 1980). Attia 1998 found no differences apart from a small difference in mean age, which was not found to be related to clinical outcome.

Inclusion of withdrawals in analysis

The majority of studies provided no information on the use of ITT analyses or otherwise. Two studies (Brambilla 1995a; Brambilla 1995b) had no withdrawals (author information) and seemed to have included all patients in analyses. Ruggiero 2001analysed data from the whole group selected for the trial (N = 35), but commented that patients who did not complete the re-feeding programme were excluded (apparently post-randomisation exclusions). Attia 1998 reported two post-randomisation exclusions that were not considered in the analyses and an additional patient who was included in the analysis whose self-report data were not analysed (as she was considered to be unreliable in terms of reporting her symptoms). However, in this study results were presented for all outcomes in the whole sample and it is unclear how much of the data from this last patient were included. Biederman 1985 did not report on withdrawals (apparently none) and analysed data from all patients for some outcomes. Halmi 1986 had withdrawals and exclusions, and did not include all patients in all analyses (e.g. scores on Hamilton Depression Scale). Lacey 1980 had drop-outs but seem to have followed-up all patients and analysed their weight gain outcomes.

Statistical analysis

Most studies had appropriate statistical analysis and two (Attia 1998; Halmi 1986) had appropriate and comprehensive statistical analysis.

Conclusions

Conclusions were judged to be justified in all studies.

Conflict of interest

Three trials acknowledged support and/or declared interests (Attia 1998; Biederman 1985; Halmi 1986).

RESULTS

The following results show that major methodological limitations of trials such as small size of samples and large confidence intervals decreased the power of studies to detect differences between treatments. Additionally, meta-analysis of data was not possible for the majority of outcomes.

Two included studies were investigated in sensitivity analysis as they were insufficient to differ from the other trials and presented lower quality information: Lacey 1980 did not provide criteria for diagnosis of AN (the sample was "patients admitted to anorectic unit at Atkinson's Morley Hospital"); Halmi 1986 presented a completion rate of 64% in the placebo arm; however, there was a "minimal early weight gain exclusion criterion" in this trial, and most of the non-completers were post-randomisation exclusions due to this criterion (13% in the drug group and 20% in the placebo group). If only later drop-outs were considered in Halmi 1986, the study had completion rates of 87% in the drug group and 88% in the placebo group.

1. Comparison antidepressants versus placebo

Four trials compared an antidepressant drug to placebo: Attia 1998; Biederman 1985; Halmi 1986; Lacey 1980.

- **Primary outcome: weight gain**

No evidence of any effect on weight gain was found for antidepressants combined with other interventions (mainly inpatient treatment) when compared to placebo.

Data on the main outcome, weight gain, were provided in many different forms and, for that reason, with the exception of the outcome number of patients achieving target weight, aggregation of data in meta-analysis was not possible. Data from individual studies were presented in graphs.

(a) End-of-treatment mean absolute weight gain or body mass index

Lacey 1980 compared clomipramine to placebo and did not find a statistically significant difference in mean weight gain (absolute weight increase in kilograms) at the end of the treatment (SMD = 0.64 95% CI -0.37 to 1.65). Although the placebo group seemed to do better during the treatment phase, at one year follow-up patients in the clomipramine group were maintaining their weight at a higher percentage of ideal weight than patients in the placebo group (even though medication had been discontinued soon after their target weights had been attained), but again the difference between groups did not reach statistical significance (SMD = -0.74 95% CI -1.77 to 0.28). Reviewers assumed that the data referred to all patients (N = 16) on both outcomes.

Attia 1998 compared fluoxetine to placebo and found no significant difference between groups (SMD = 0.14 95% CI -0.56 to 0.85) in mean percentage of ideal weight at the end of treatment.

(b) Number of patients achieving target weight or weight within the normal range
(presented in negative form in the graphs: number of patients NOT achieving target weight)

Information on the number of patients who achieved target weight could be extracted from three studies (Attia 1998; Halmi 1986; Lacey 1980). However, the reviewers considered that differences in characteristics of the studies precluded us from grouping data of one of the studies (Lacey 1980) with the other two (Attia 1998; Halmi 1986) for this outcome measure. Lacey 1980 did not establish a time to achieve normal weight, while the other two studies determined a maximum duration of treatment (90 days in the Halmi 1986 study and seven weeks in the Attia 1998 trial) and reported the number of patients who were able to reach the target during this time period. Lacey 1980 reported a mean time of 10 weeks for all patients of the study to achieve weight within normal range, including the drop-outs. In the other two trials (Attia 1998; Halmi 1986), those who did not drop out or were excluded took a mean time of five weeks to reach target weight. Thus, it did not seem appropriate for us to combine data from studies that applied different methods to estimate improvement in weight gain and had different time scales for reaching target weight.

Meta-analysis of data on the number of patients not achieving target weight (N = 79) from the two studies (Attia 1998; Halmi 1986) with a more similar design did not show a significant difference in efficacy between antidepressant treatment and placebo (RR = 0.83 95% CI 0.41 to 1.67; Z = 0.53, P = 0.60) in helping patients to achieve a weight within the normal range (target weight) during the brief time period of the trials. Sensitivity analysis was planned for any meta-analysis that included the Halmi 1986 trial (as stated earlier) but this meta-analysis had only two trials and heterogeneity was not identified between studies (I^2 = 0%).

As stated above, all patients in the third study (Lacey 1980) reached target weight (including drop-outs) and thus, no difference in efficacy was evident from use of antidepressants.

(c) Mean rate of weight gain

Two studies investigated the rate of weight gain, measuring the increase in kilograms per day of treatment with antidepressants (tricyclics) compared to placebo (Halmi 1986; Lacey 1980). The estimates of effect were in opposite directions in these two trials and as considerable heterogeneity was found when meta-analysis of data was tried (I^2 = 83.4%) reviewers considered that the data would be better presented independently.

The possible explanations raised for the heterogeneity found between these studies are:
(i) differences in treatment due to its mean duration (as discussed in the previous item), the antidepressant doses used (higher in the Halmi 1986 trial, amitriptyline 160mg per day versus clomipramine 50mg per day in the Lacey 1980 trial), the combined inpatient treatments offered;
(ii) data on the Halmi trial were relative only to those who gained minimal weight at the beginning of treatment and managed to remain in trial: these patients could be at a higher baseline weight for example (information not available for comparison) and with greater chances of having an antidepressant effect;
(iii) very small sample size in the Lacey 1980 trial (N = 16);
(iv) differences in patient selection, as diagnosis of AN was not based on rigorous criteria in the Lacey 1980 trial.

Halmi 1986 found that the daily rate of weight increase was higher in the drug group (amitriptyline) but the difference was not statistically significant (SMD = -0.53 95% CI -1.22 to 0.17). These data referred only to patients that achieved target weight (33/48), excluding non-completers for any reason (and those who failed to achieve minimal weight gain in the first six weeks of trial). In the Lacey 1980 trial, the daily rate of weight gain tended to be greater in the placebo group (SMD = 1.07 95% CI 0.00 to 2.14) when the total number of the randomised patients (N = 16) in the study were considered (although information relative to number of patients for this data was not available and was inferred by the reviewers). In the paper, the authors (Lacey 1980) stated that the difference in body weight gained each day was not statistically significant.

Attia 1998 also analysed rate of weight gain reflected by the change in percent of ideal body weight per day, but no differences were found between fluoxetine and placebo (SMD = 0.48 95% CI -0.24 to 1.20).

(d) Time to achieve target weight (ideal, weight within normal range)

Again, data from the two studies (Halmi 1986; Lacey 1980) that reported on mean days to achieve target weight were not aggregated for the reasons stated above (differences in studies characteristics discussed in the two earlier items). Neither trial found any significant difference between antidepressants and placebo in time to achieve target weight.
Halmi 1986 considered only patients who achieved their target weight (33/48) and found a SMD of -0.70 (95% CI - 1.40 to 0.01). The Lacey 1980 trial found a SMD of 0.15 (95% CI -0.84 to 1.13). This calculation was made on the total number of randomised patients (N = 16).

(e) Any other measure of change in weight

In the Biederman 1985 trial there was no significant difference (RR = 1.08 95% CI 0.93 to 1.25) in the number of patients who did not manage to increase more than 30% of their baseline weight during treatment with amitriptyline compared to placebo (five weeks).

- **Secondary outcomes**

1. Efficacy in reducing eating disorders symptoms, associated psychopathology and improving clinical global state.

Antidepressants did not differ from placebo in terms of reducing eating disorder and associated psychopathology, nor in improving global clinical state.

(a) Eating disorder symptomatology

In the Attia 1998 trial we found no evidence for efficacy of fluoxetine in reducing eating disorders symptoms as measured by end-of-treatment mean scores on either of the following scales:

Anorectic Behaviour Scale (SMD = -0.11 95% CI -0.82 to 0.59); Yale-Brown-Cornell Eating Disorder Scale (SMD = 0.17 95% CI -0.54 to 0.87); Eating Attitudes Test (SMD = 0.33 95% CI -0.38 to 1.04) and Body Shape Questionnaire (SMD = -0.28 95% CI -0.98 to 0.43).

(b) Recovery

No study provided this data except for Lacey 1980; however authors provided mean scores without reporting standard deviations and it was not possible to use the data.

(c) Level of depressive symptoms

Biederman 1985 reported on the number of patients not presenting greater than 50% improvement in depressive symptoms evaluated with the antidepressant scale of the SADS-C: RR of 1.27 (95% CI 0.97 to 1.67) no significant difference between antipressant (amitriptyline) and placebo.

As there were missing data in this outcome, the reviewers adopted ITT principles and considered these patients as unimproved, and data are presented including them. Sensitivity analysis comparing ITT analysis, and analysis based on the number of analysed patients showed similar results (both not significant).

A meta-analysis of data from two studies (Attia 1998; Halmi 1986) (N = 79) evaluating reduction in depressive symptoms through end-point mean scores in Beck Depression Scale (where groups were comparable at baseline in both studies, tested by reviewers) did not find an advantage for antidepressant treatment (SMD = 0.01 95% CI -0.43 to 0.45; overall effect Z = 0.05, P = 0.96). Sensitivity analysis (as planned) was not performed as there were only two trials but no heterogeneity was found between studies (I^2 = 0%).

Attia 1998 evaluated improvement in depressive symptoms using end-point mean scores in the depression subscale of the SCL-90, and did not find any differences (SMD = 0.11 95% CI -0.60 to 0.81) between groups. Halmi 1986 analysed depressive symptoms comparing end-point mean scores of Hamilton Depression Scale, but also did not find a statistically significant difference (SMD = -0.45 95% CI -1.12 to 0.22); moreover data in this outcome did not refer to all randomised patients (36/48) and reviewers were not able to apply ITT principles as no additional information could be obtained from the authors.

(d) Level of anxiety symptoms (including obsessive-compulsive symptoms)

Biederman 1985 did not find any difference in the number of patients failing to present greater than 50% improvement in obsessional symptoms evaluated with the HSCL (RR = 1.08 95% CI 0.93 to 1.25), and in anxiety symptoms evaluated with the SADS-C (RR = 1.17 95% CI 0.94 to 1.44). ITT principles were applied to missing data in both outcome measures, in that patients with missing data were assumed not to have improved. Sensitivity analysis comparing ITT analysis and analysis based on the number of evaluated patients showed no difference in results (both not significant).

Attia 1998 also reported on improvement in obsessional symptoms based on end-point mean scores in the obsessive-compulsive subscale of the SCL-90 (comparable baseline scores between groups) but did not detect any effect of fluoxetine (SMD = 0.25 95% CI -0.46 to 0.96).

(e) Clinical Global Improvement

Biederman 1985 compared clinical global effect of amytriptyline versus placebo, but found no difference between groups as measured by number of patients not reporting greater than 50% improvement on the Clinical Global Scale (RR = 0.98 95% CI 0.77 to 1.24).

One study (Attia 1998) provided end-point mean scores in Clinical Global Improvement. Statistical analysis did not identify any effect of antidepressant (fluoxetine) in improving clinical global state (SMD = -0.20 95% CI -0.91 to 0.51).

2. Acceptability of treatment

This review did not find any evidence of differential acceptability of antidepressants when compared to placebo as measured by the following outcomes:

(a) Proportion of non-completers (drop-outs) due to any reason

Meta-analysis of drop-outs for any reason was performed and no difference was found in overall non-completion rates in groups receiving antidepressant treatment compared to those receiving placebo. Four studies were considered (Attia 1998; Biederman 1985; Halmi 1986; Lacey 1980) (N = 120), and 12 out of 57 patients in the antidepressants group did not complete the trials, compared to 14 out of 63 patients in the placebo group who left the study before its end (RR = 0.90 95% CI 0.46 to 1.75; overall effect Z = 0.32, P = 0.75).

Reviewers assumed there were no drop-outs in the Biederman 1985 study.

ITT analysis was not performed by reviewers as it was not possible to identify group assignment of one of the two patients excluded post-randomisation in the Attia 1998 trial.

(b) Proportion of non-completers due to adverse effects

Aggregation of data of all placebo-controlled trials (Attia 1998; Biederman 1985; Halmi 1986; Lacey 1980) in meta-analysis (N = 120) found no significant difference in the numbers of patients leaving the treatment because of side-effects, thus no difference in acceptability of treatment due to adverse effects could be demonstrated in this review (RR = 0.66 95% CI 0.09 to 4.82; overall effect Z = 0.42, P = 0.68). Again reviewers assumed that no drop-outs for side effects occurred in the Biederman 1985 (the authors reported on side-effects but not on drop-outs for that reason). Again, ITT analysis was not performed by reviewers as it was not possible to identify group assignment of one of the two patients excluded post-randomisation in the Attia 1998 study.

(c) Number of subjects reporting side effects

This information could only be extracted from one study (Attia 1998), which found no difference between the number of patients reporting side-effects on antidepressant treatment or placebo (RR = 2.13 95% CI 0.22 to 21.17).

2. Comparison antidepressant versus antidepressant

Three studies were included in this comparison (Brambilla 1995a; Brambilla 1995b; Ruggiero 2001).

- **Primary Outcome : weight gain**

(a) End-of-treatment mean absolute weight gain or body mass index

No evidence was found of greater efficacy for any antidepressant compared to another antidepressant, when used in combination with other types of interventions.

Brambilla 1995a and Brambilla 1995b compared fluoxetine to nortriptyline and to amineptine. In both studies no statistical difference was found in end-of-treatment mean BMI between different antidepressants; the SMD found for the fluoxetine versus amineptine comparison was -0.68 (95% CI -1.81to 0.46) and for the fluoxetine versus nortriptyline comparison was 0.81 (95% CI -0.12 to 1.75).

Ruggiero 2001 tested the efficacy of fluoxetine against clomipramine but did not find greater efficacy for either drug in improving weight gain as measured by end-of-treatment mean absolute weight (SMD = -0.45 95% CI -1.28 to 0.39) or mean percent of weight increase (SMD = -0.19 95% CI -1.02 to 0.63).

(b) Other measures of weight gain: not available for this group of studies.

- **Secondary outcomes**

(a) Eating disorder symptoms: one study found amineptine had a greater effect on eating disorder symptoms compared to fluoxetine (Brambilla 1995b).

Two studies (Brambilla 1995a; Brambilla 1995b) used the Eating Disorders Inventory scores to evaluate improvement in eating disorders symptoms in the trials: in one of the studies (Brambilla 1995b) amineptine was superior to fluoxetine in reducing eating disorder symptoms (SMD = 1.70 95% CI 0.36 to 3.04; overall effect Z = 2.48, P = 0.01); the second study, comparing fluoxetine versus nortriptyline (Brambilla 1995a) did not identify differences between antidepressants in relation to eating disorder symptoms (SMD = 0.09 95% CI -0.81to 0.99).

(b) Level of depression: no difference between tested antidepressant drugs.

Depressive symptoms were evaluated in Brambilla 1995a and Brambilla 1995b using end-point mean scores on the Hamilton Depression Scale. No difference was found between the comparisons in terms of reduction of depressive symptoms: fluoxetine versus nortriptyline (SMD = 0.86 95% CI -0.08 to 1.80) and fluoxetine versus amineptine (SMD = 0.00 95% CI -1.09 to 1.09).

(c) Level of anxiety: one study found a greater efficacy of nortriptyline compared to fluoxetine in reducing anxiety (Brambilla 1995a).

Anxiety symptoms were also evaluated in two studies (Brambilla 1995a; Brambilla 1995b) through end-point mean scores on the Hamilton Anxiety Scale. Nortriptyline showed greater efficacy compared to fluoxetine in reducing anxiety symptoms (Brambilla 1995a), with a SMD of 1.28 (95% CI 0.29 to 2.27; overall effect Z = 2.53, P = 0.01). The comparison of fluoxetine versus amineptine did not identify any difference (SMD = 0.38 95% CI - 0.72 to 1.48).

Finally, subgroup analysis comparing different classes of antidepressants or setting of treatment were not performed due to the

small number of trials and methodological limitations to aggregation of data.

DISCUSSION

This systematic review aimed to evaluate the existing evidence on the efficacy and acceptability of antidepressant treatment in the acute phase of AN. It is clear from the review that there is a lack of quality of information in this field that severely compromises interpretation of results.

Methodological considerations

The numerous methodological limitations of the trials included might have accounted for the findings of this review. To start, a very small number of studies have been performed to date comparing antidepressants to placebo, limiting the available data. Considering the quality of assessment, none of the studies gave details on concealment of randomisation allocation and none reported on testing for the integrity of blinding. Nevertheless, as no evidence of efficacy of drug treatment has been found, bias due to inadequate allocation concealment and/or blinding does not seem to have occurred or to have affected results in terms of increasing the chance of overestimation of drug effect.

The greatest limitation of the studies was the very small sample size of all trials (e.g. eight patients in each arm of one trial), as it led to decreased power to detect differences in effects, shown in the results by the large confidence intervals found in most analyses. As expected, no trial of the placebo comparisons investigated antidepressants as the sole treatment, which would be outside current clinical practice guidelines (APA 2000; NCCMH 2004). However, this might have been another important limitation of the studies, the combination of antidepressants with multiple psychological and nutritional inpatient interventions (including behavioural programmes devoted to weight gain) i.e. an intensive care that usually promotes weight restoration by itself. In such a condition, the effect that a drug added to this whole "package" of treatment is able to contribute, for instance in terms of increase in the rate of weight gain, is likely to be small and difficult to demonstrate; if we also take into account the small sizes of trials, the power of these studies to detect even large differences in effects is definitely compromised.

Another important methodological flaw of the placebo-controlled trials included here were their short length, some with planned or mean duration of around five weeks and no follow-up period; this period is too short to evaluate the effect of an antidepressant in a disorder with psychopathological disturbances of enduring nature and a typically slow course of recovery. Additionally, some trials used low or moderate doses of antidepressants and some did not refer to testing compliance with drug treatment, a possible problem with patients with AN, who are usually reluctant to take medicines.

Other methodological shortcomings of trials involved the outcome measures and reporting of outcomes. The primary outcome in this review was improvement in weight gain, as it is considered a first and essential step in recovering from AN, as is a reliable outcome measure. Most of the trials had weight gain as the primary outcome; however, the way this was reported varied between studies, preventing aggregation of the results. It would be useful if trials systematically reported the number of patients achieving normal weight at the end of the trial, as weight restoration to normal seems to be associated with better outcomes (Baran 1995; Agras 2004), and can be easily reported and further aggregated. The same problem occurred with secondary outcome measures: different scales were used or different ways of reporting data prevented us from performing meta-analysis of data. The use of dichotomous data, such as the number of patients presenting end-of-treatment scores below the scale cut-off point, or the use of categories of levels of improvement in symptoms would facilitate further aggregation of results.

Additionally, other problems identified in studies were that the presentation of data on completion rates and on numbers of patients evaluated for each outcome variable were not always available. Authors also rarely performed ITT analyses.

Heterogeneity was found between studies. Two main reasons for this could be that studies were found to be pursuing similar objectives (improvement in the treatment of acute AN) but with possible differences in goals and in expected actions of the antidepressants. Differences in definition of an adequate time scale for weight rehabilitation (or no definition at all) may have led to different results, as observed in terms of the mean duration of treatments (in Lacey 1980 the mean duration of treatment was twice that of the mean durations in the Attia 1998 and Halmi 1986 studies); secondly, different "packages" of treatment combined with drugs may result in poorly comparable interventions.

Finally, another aspect that can impact on treatment outcome (but was not evaluated in this review) is patient variability (such as age and illness factors). Biederman 1985 had a younger sample than other placebo-controlled trials; as in other disorders, presentation at early onset of the disorder (before 18 years of age) may have a better outcome (Strober 1997b), but longer periods of follow-up are required to evaluate this. Case-mix in terms of sub-type of AN (binge-purge or restrictor) is another aspect that may have an impact when evaluating a drug, as biological differences may lead to different effects (Kaye 1999a; Kaye 1999b); however, samples of the placebo comparisons had mixed types of AN patients, and only one trial investigated efficacy of drugs by AN sub-type (Halmi 1986).

Main findings

A comprehensive search of the literature was conducted in order to identify RCTs that tested antidepressants in the treatment of acute AN, but only seven studies were found to fulfill crite-

ria for this review, four of them comparing antidepressant treatment to placebo. Although patients showed improvement during treatments in most studies, usually with significant changes in weight compared to baseline, the RCTs included here were not able to demonstrate any effect of antidepressant drugs compared to placebo in the majority of the outcomes considered in this review. The only positive findings in this review were a greater effect of amineptine compared to fluoxetine in reduction of eating disorder symptoms evaluated through end-of-treatment Eating Disorders Inventory mean scores, and greater effect of nortriptyline compared to fluoxetine in reducing anxiety symptoms measured through Hamilton Anxiety Scale mean scores. However, these were isolated findings, of unclear significance in light of the findings from the placebo comparisons; for that reason, they should not be conceived as evidence of efficacy of a specific drug or class of antidepressant. The authors of the present review expected that aggregation of data from trials would increase the power to detect differences in efficacy between tested drugs (or placebo), as pharmacotherapy trials in AN were few and of small sizes; however, aggregation of data in meta-analysis was not possible for the majority of outcomes in this review. The only efficacy outcome in which meta-analysis (with data from two trials) was done was with the number of patients not achieving target weight, but evidence of effect of antidepressants could not be demonstrated.

In the trials included in this review, drugs with different profiles of pharmacological action have been tested: amitriptiline (both noradrenergic and serotonergic), clomipramine (mainly serotonergic), fluoxetine (selective serotonergic), nortriptiline (mainly noradrenergic) and amineptine (mainly dopaminergic). Researchers seem to have tried to target different goals through different expected action of drugs. As mentioned earlier, serotonergic deregulation has been demonstrated in AN (Kaye 1991a; Kaye 1998; Frank 2001b; Attia 2005) and considered a predisposing factor for developing the illness. It has been postulated that serotonin modulates the balance between dopamine, noradrenaline and GABA (the aminobutyric acid), which mediate, respectively, thought processes, anxiety and mood; the homeostasis of these neurotransmitters are thought to be disturbed in the illness, and serotonergic drugs are expected to reinstate the homeostasis (Vaswani 2004). Moreover, the neurotransmitter systems are all involved in the complex neurobiological control of weight and food intake (Appolinario 2004). Reduced serotonergic neurotransmission and compensatory receptor activation (functional supersensitivity of 5-HT2c receptors) due to dieting have been associated with increased food consumption and weight gain (Kaye 1991c; Cowan 1996). Other authors considered that a decrease in hypothalamic noradrenergic activity could be involved in AN and that tricyclic antidepressants could enhace food intake/appetite through stimulation of alpha-noradrenergic receptors within the medial hyphotalamus (Pirke 1996; Appolinario 2004; Leibowitz 1986). Brambilla 1995b however, tested amineptine to inhibit hunger in binge-purge AN patients through its dopaminergic-stimulating effect, in contrast with the current, renewed interest in antipsychotic drugs (the atypicals) to treat acute AN, that is based on the dopaminergic deregulation hypothesis and the appetite-stimulating side-effect of these drugs (through blockade of dopamine receptors in the ventromedial nucleus) (Bosanac 2005).

It has been suggested that the neurochemical abnormalities of the malnourished state may partially explain the clinical non-response to drugs, especially SSRIs, observed in the acute phase of AN (Attia 1998; Kaye 1998; Attia 2005). In fact, decreased levels of CSF 5-HIAA, noradrenaline (NE) and 3-methoxy-4-hydroxyphenylglycol (MHPG), and HVA have all been reported in studies (Kaye 1984; Pirke 1996; Kaye 1998). The low levels of CSF 5-HIAA detected in AN underweight patients may be possibly related to the poor dietary intake of tryptophan (the precursor of serotonin). Moreover, low values of oestrogen during the malnourished state and low intake of other nutrients (essential fatty acids, zinc, pyridoxine) that are believed to influence serotonin pathway function may also impair neuronal release of 5-HT in the brain, down-regulate its receptor, and thus, reduce the antidepressant action. Attia 2005 measured plasma tryptophan (TRP) and the ratio TRP/LNAA (large neutral amino acids) in AN during re-feeding, and found levels to be low at baseline, but to increase gradually towards normalisation with weight restoration. In a recent RCT, however, this finding of lack of response to SSRI medication due to inadequate supply of nutrients has been contested as nutritional supplementation (including tryptophan) or placebo nutritional supplements were added to fluoxetine and it was found that nutritional supplements did not increase efficacy of fluoxetine treatment in underweight AN patients (Barbarich 2004); however, a small sample size and high attrition rate limit the interpretation of results.

Although limited by the poor quality of evidence available, the findings of antidepressant trials in acute AN have raised the discussion of whether research testing these drugs during the starvation state should go on. The use of antidepressant drugs have then been considered in weight-restored patients, when the effects of malnutrition are beign resolved. In this stage, medications could be used to treat remaining depressive and obsessive-compulsive symptoms, and to prevent relapse (weight loss). Preliminary positive findings in this field support the indication of SSRIs (fluoxetine) to prevent relapse in AN (Kaye 1991b; Kaye 2001b), but negative findings have all been reported (Strober 1997a). This is certainly an area that should be further explored.

Apart from the unproven efficacy of antidepressants, issues of safety and acceptability of drug treatment in AN also have to be considered. Previous studies in bulimia nervosa from our group (Bacaltchuk 2005) have found relatively high rates of treatment drop-out with antidepressant therapy compared to low rates with psychotherapy. In this review, it was possible to perform meta-analysis of non-completion rates in trials. Despite the reported side-effects by patients treated with antidepressant drugs (especially tricyclics)

in some trials (Biederman 1985; Halmi 1986), no significant difference in drop-outs from studies (for any reason or for side-effects) was detected of tested antidepressants compared to placebo. While still widely used in developing countries (for economic reasons), tricyclics are associated with uncomfortable adverse effects and increased cardiac risks as prolongation of the QT interval (and arrhythmias) can occur. As some AN patients (especially those who purge and develop hypokalaemia) may also present with a prolonged QT interval, tricyclics are likely to be contra-indicated in underweight AN patients (Ackerman 1998; Reilly 2000) and new trials testing them are not expected to be developed. Newer drugs, with safer and better side-effect profiles such as SSRIs, are considered a better options, though they could not prove to be of benefit until the moment. However, results from open label studies (Pallanti 1997; Fassino 2002; Santonastaso 2001; Ruggiero 2003) have suggested improvement with SSRIs, and the methodological limitations (discussed below) of the trials presented in this review compromise the clear understanding of the role of these drugs in acute AN. It is expected that an improved knowledge of the neurochemical alterations of the starvation state of AN can give clues to pharmacological research in this phase of the illness.

AUTHORS' CONCLUSIONS

Implications for practice

Anorexia nervosa is a complex disorder that challenges clinicians and researchers who wish to improve its treatment. In line with what is commonly reported in the literature in the field (Treasure 2004; De Zwann 2003a) this systematic review could not find evidence of efficacy of antidepressants in the acute phase of AN. A lack of quality information precludes us from drawing definite conclusions or recommendations on the use of these drugs in this phase of the illness. It is likely that short term treatment of underweight patients with antidepressants does not confer added benefit over and above specialised inpatient treatment, as most patients responded to complex inpatient programmes that targeted weight gain in trials. However, it needs to be noted that many patients with AN are treated as outpatients, with less intensive input, or outside specialised services, and antidepressants have not been tested in such conditions.

Moreover, although improved, many patients remain clinically symptomatic following re-feeding in hospital (Attia 1998), and are highly vulnerable to relapse. Unlike the findings in this review, promising initial results have been achieved by studies that investigated fluoxetine for relapse prevention in weight restored AN patients (Kaye 1991a; Kaye 2001a). Although these findings need replication, it suggests that the use of antidepressants could be considered after weight has been at least partially restored, aiming at improvement of residual symptoms and prevention of weight loss at follow-up.

Nevertheless, the regulatory agencies in United Kingdom (MHRA) and United States (FDA) have not approved any medication for the treatment of AN. Additionally, they have recently examined the controversial issue of the existence of a possible link between suicidality and use of antidepressants in children and adults, and they found that there was no, or insufficient, evidence from clinical trials to demonstrate that benefits of treating depressive illness in patients under 18 years of age with SSRIs outweighs the risks of side-effects, with the exception of fluoxetine, that was identified to have a positive balance. Thus, fluoxetine is the only approved drug in UK and US for treatment of depression in children (although recently it has been shown to be also associated with increased suicidal behaviour). In a critical appraisal of the subject, Licinio 2005 states that "most people who commit suicide suffer from major depression disorder, and in the vast majority of cases their suicide is the result of untreated or inadequately treated depression". Authors also state that "warnings from the agencies are not intended to prohibit the use of antidepressants, but to encourage prescribers to balance this risk versus the clinical need and the long-term consequences of not treating depression or other psychiatric disorders in children and adolescents". It is advisable, of course, to take all possible safety measures when antidepressants are used.

Implications for research

Although considerable research has been devoted to understanding AN, little progress has been made in developing effective treatments for this disorder and there is currently no single leading treatment for AN (NCCMH 2004; Agras 2004; Fairburn 2005). As seen in this review, the trials that investigated antidepressants in acute AN had major limitations that were mainly due to the small sample sizes (insufficient power to detect differences, large confidence intervals), and setting of treatment (inpatient complex programmes).

Thus, a randomised trial with a naturalistic design, comparing drug plus routine clinical practice (e.g. psychotherapy that includes nutritional advice) and routine clinical practice without medication in outpatient settings, could address the methodological pitfalls raised so far if the following aspects are also considered: (a) as inadequate sample sizes may have precluded finding meaningful differences between treatment groups, it is therefore paramount to have multi-centre trials with a large number of participants; (b) patients with AN need individualised interventions. The impact of treatment variations should be evaluated in analysis; (c) the study should have a long duration so as to assess the full spectrum of consequences and outcomes of these treatments; (d) the primary outcome should focus on the proportion of patients achieving normal BMI, and (e) as pointed out by the NIH report on "Overcoming barriers to treatment research in AN", secondary outcomes should include both measures of core and associated symptoms as well as measures of quality of life, social adaptation and resource utilization (Agras 2004). The blinding of the outcome assessments

could be done by masking the research interviewers to the aims of the study. This study design may lead to numbers participating, fewer drop-outs and improved compliance.

Despite the existing controversy with utility of pharmacological agents during the starvation state of AN, drug trials are still needed as definitive conclusions on efficacy cannot yet be made. Moreover, specialist treatment is expensive and not widely available. Given the clinical problems and cardiac risks associated with tricyclic antidepressants, it is advisable that further trials test safer and more tolerable antidepressants such a SSRIs, noradrenergic specific agents and non tricyclic dual reuptake antidepressants to help inform clinical practice. It is also expected that increased knowledge on the neurobiology of AN might favour the development of more specific pharmacological targets in the treatment.

POTENTIAL CONFLICT OF INTEREST

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REFERENCES

References to studies included in this review

Attia 1998 *{published data only}*
Attia E, Haiman C, Walsh BT, Flater SR. Does fluoxetine augment the inpatient treatment of anorexia nervosa?. *American Journal of Psychiatry* 1998;155(4):548–51.

Biederman 1985 *{published data only}*
Biederman J, Herzog DB, Rivinus TM, Harper GP, Ferber RA, Rosenbaum JF, et al. Amitriptyline in the treatment of anorexia nervosa: a double-blind, placebo-controlled study. *Journal of Clinical Psychopharmacology* 1985;5(1):10–6.

Brambilla 1995a *{published and unpublished data}*
Brambilla F, Draisci A, Peirone A, Brunetta M. Combined cognitive-behavioral, psychopharmacological and nutritional therapy in eating disorders: anorexia nervosa restricted type. *Biological Psychiatry* 1995; 32:59–63.

Brambilla 1995b *{published and unpublished data}*
Brambilla F, Draisci A, Peirone A, Brunetta M. Combined cognitive-behavioral, psychopharmacological and nutritional therapy in eating disorders: anorexia nervosa binge-eating/purging type. *Biological Psychiatry* 1995;32:64–7.

Halmi 1986 *{published data only}*
Halmi KA, Eckert E, LaDu TJ, Cohen J. Anorexia nervosa. Treatment efficacy of cyproheptadine and amitriptyline. *Archives of General Psychiatry* 1986;43(2):177–81.

Lacey 1980 *{published data only}*
Crisp AH, Lacey JH, Crutchfield M. Clomipramine and 'drive' in people with anorexia nervosa: an in-patient study. *British Journal of Psychiatry* 1987;150:355–8.

* Lacey JH, Crisp AH. Hunger, food intake and weight: impact of clomipramine on a refeeding anorexia nervosa population. *Postgraduate Medical Journal* 1980;56 Suppl 1:79–85.

Ruggiero 2001 *{published data only}*
Ruggiero GM, Laini V, Mauri MC, Ferrari VM, Clemente A, Lugo F, et al. A single blind comparison of amisulpride, fluoxetine and clomipramine in the treatment of restricting anorectics. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2001;25(5): 1049–59.

References to studies excluded from this review

Barbarich 2004
Barbarich NC, McConaha CW, Halmi KA. Use of nutritional supplements to increase the efficacy of fluoxetine in the treatment of anorexia nervosa. *International Journal of Eating Disorders* 2004;35 (1):10–5.

Bergh 1996
Bergh C, Eriksson M, Lindenberg G, Sodersten P. Selective serotonin reuptake inhibitors in anorexia. *Lancet* 1996;348:1459.

Bergh 2002
Bergh C, Brodin U, Lindberg G, Södersten P. Randomized controlled trial of a treatment for anorexia and bulimia nervosa. *Proceeding of the National Academy of Sciences of USA* 2002;99(14):9486–91.

Birmingham 1994
Birmingham CL, Goldner EM, Bakan R. Controlled trial of zinc supplementation in anorexia nervosa. *International Journal of Eating Disorders* 1994;15(3):251–5.

Brambilla 1995c
Brambilla F, Draisci A, Peirone A, Brunetta M. Combined cognitive-behavioral, psychopharmacological and nutritional therapy in bulimia nervosa. *Neuropsychobiology* 1995;32(2):68–71.

Calandra 1999
Calandra C, Gulino V, Inserra L, Giuffrida A. The use of citalopram in an integrated approach to the treatment of eating disorders: an open study. *Eating and Weight Disorders* 1999;4(4):207–10.

Corwin 1995
Corwin J, Connelly S, Paz S, Schwartz M, Wirth J. Chart review of rate of weight gain in eating disorder patients treated with tricyclic antidepressants or fluoxetine. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 1995;19(2):223–8.

Eckert 1987
Eckert ED, Halmi KA, Marchi P, Cohen J. Comparison of bulimic and non-bulimic anorexia nervosa patients during treatment. *Psychological Medicine* 1987;17:891–9.

Falk 1985
Falk JR, Halmi KA, Tryon WW. Activity measures in anorexia nervosa. *General Hospital Psychiatry* 1985;42:811–4.

Fassino 2002
Fassino S, Leombruni P, Daga GA, Brustolin A, Migliaretti G, Cavallo F, et al. Efficacy of citalopram in anorexia nervosa: a pilot study. *European Neuropsychopharmacology* 2002;12:453–9.

Ferguson 1987
Ferguson JM. Treatment of an anorexia nervosa patient with fluoxetine. *American Journal of Psychiatry* 1987;144(9):1239.

Ferguson 1999
Ferguson CP, La Via MC, Crossan PJ, Kaye WH. Are serotonin selective reuptake inhibitors effective in underweight anorexia nervosa?. *International Journal of Eating Disorders* 1999;25(1):11–7.

Frank 2001a
Frank GK, Kaye WH, Marcus MD. Sertraline in underweight binge eating/purging-type eating disorders: five case reports. *International Journal of Eating Disorders* 2001;29(4):495–8.

Gross 1981
Gross HA, Ebert MH, Faden VB, Goldberg SC, Nee LE, Kaye WH. A double-blind controlled trial of lithium carbonate in primary anorexia nervosa. *Journal of Clinical Psychopharmacology* 1981;1(6):376–81.

Gwirtsman 1990
Gwirtsman HE, Guze BH, Yager J, Gainsley B. Fluoxetine treatment of anorexia nervosa: an open clinical trial. *Journal of Clinical Psychiatry* 1990;51(9):378–82.

Halmi 1982
Halmi KA, Eckert E, Falk JR. Cyproheptadine for anorexia nervosa. *Lancet* 1982;1(8285):1357–8.

Halmi 1983
Halmi KA, Eckert E, Falk JR. Cyproheptadine, an antidepressant and weight-inducing drug for anorexia nervosa. *Psychopharmacology Bulletin* 1983;19(1):103–5.

Halmi 1999
Halmi K, Mitchell J, Crow S. Fluoxetine vs cognitive behavioral therapy in relapse prevention for anorexia nervosa. *Journal of the European College of Neuropsychopharmacology* 1999;9 Suppl 5:S373.

Holtkamp 2005
Holtkamp K, Konrad K, Kaiser N, Ploenes Y, Heussen N, Grzella I, et al. A retrospective study of SSRI treatment in adolescent anorexia nervosa: insufficient evidence for efficacy. *Journal of Psychiatric Research* 2005;39:303–10.

Hudson 1985
Hudson JI, Pope HG, Jonas JM, Yurgelun-Todd D. Treatment of anorexia nervosa with antidepressants. *Journal of Clinical Psychopharmacology* 1985;5(1):17–23.

Kaye 1991b
Kaye WH, Weltzin TE, Hsu LKG, Bulik CM. An open trial of fluoxetine in patients with anorexia nervosa. *Journal of Clinical Psychiatry* 1991;52(11):464–71.

Kaye 2001b
Kaye WH, Nagata T, Weltzin TE, Hsu LK, Sokol MS, McConaha C, et al. Double-blind placebo-controlled administration of fluoxetine in restricting - and restricting-purging-type anorexia nervosa. *Biological Psychiatry* 2001;49:644–52.

Moore 1977
Moore DC. Amitriptyline therapy in anorexia nervosa. *American Journal of Psychiatry* 1977;134(11):1303–4.

Mumford 1984
Munford PR, Tarlow G, Gerner R. An experimental analysis of the interaction of chemotherapy and behavior therapy in anorexia nervosa. *Journal of Nervous and Mental Disease* 1984;172(4):228–31.

Pallanti 1997
Pallanti S, Quercioli L, Ramacciotti A. Citalopram in anorexia nervosa. *Eating and Weight Disorders* 1997;2(4):216–21.

Ricca 1999
Ricca V, Mannucci E, Paionni A, Di Bernardo M, Cellini M, Cabras PL, et al. Venlafaxine versus fluoxetine in the treatment of atypical anorectic outpatients: a preliminary study. *Eating and Weight Disorders* 1999;4:10–4.

Ruggiero 2003
Ruggiero GM, Mauri MC, Omboni AC, Volonteri LS, Dipasquale S, Malvini L, et al. Nutritional management of anorexic patients with and without fluoxetine: 1-year follow-up. *Progress in Neuropsychopharmacology and Biological Psychiatry* 2003;27:425–30.

Sanchez 1993
Rey Sanchez F, Sanchez Iglesias S, Samino Aguado FJ, Lorenzo Bragado MJ, Perez Urdaniz. Fluvoxamine: An alternative pharmacological treatment in anorexia nervosa. *Revista de Psiquiatria Infanto-Juvenil* 1993;2:111–7.

Santonastaso 2001
Santonastaso P, Friederici S, Favaro A. Sertraline in the treatment od restricting anorexia nervosa: an open controlled trial. *Journal of Child and Adolescent Psychopharmacology* 2001;11(2):143–50.

Strobel 2004
Strobel M, Warnke A, Roth M, Schulze U. Paroxetine versus clomipramine in female adolescents suffering from anorexia nervosa

and depressive episode: a retrospective study on tolerability, reasons for discontinuing the antidepressive treatment and different outcome measurements. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie* 2004;32(4):279–89.

Strober 1997a
Strober M, Freeman R, DeAntonio M, Lampert C, Diamond J. Does adjunctive fluoxetine influence the post-hospital course of restrictor-type anorexia nervosa? A prospective, longitudinal follow up and comparison with historical controls. *Psychopharmacology Bulletin* 1997;33(3):425–31.

Strober 1999
Strober M, Pataki C, Freeman R, DeAntonio M. No effect of adjunctive fluoxetine on eating behavior or weight phobia during inpatient treatment of anorexia nervosa: an historical case-control study. *Journal of Child and Adolescent Psychopharmacology* 1999;9(3):195–201.

Vandereycken 1984
Vandereycken W. Neuroleptics in the short-term treatment of anorexia nervosa, a double-blind placebo-controlled study with sulpiride. *British Journal of Psychiatry* 1984;144:288–92.

Additional references

Aalto-Setala 2001
Aalto-Setala T, Marttunnen M, Tuulio-Henriksson A, Poikolainen K, Lonnqvist J, et al. One-month prevalence of depression and other DSM-IV disorders among young adults. *Psychological Medicine* 2001; 31:791–801.

Ackerman 1998
Ackerman MJ. The long QT syndrome:ion channel diseases of the heart. *Mayo Clinic Proceedings* 1998;73:250–69.

Agras 2004
Agras WS, Brandt HA, Bulik CM, Dolan-Sewell R, Fairburn CG, Halmi KA, et al. Report of the National Institutes of Health Workshop on Overcoming Barriers to Treatment Research in Anorexia Nervosa. *International Journal of Eating Disorders* 2004;35:509–21.

Anderluh 2003
Anderluh MB, Tchanturian K, Rabe-Hesketh S, Treasure J. Childhood obsessive-compulsive personality traits in adult women with eating disorders: defining a broader eating disorders phenotype. *American Journal of Psychiatry* 2003;160:242–247.

APA 2000
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. 4th - Text Revision Edition. Washington, DC: American Psychiatric Association, 2000.

Appolinario 2004
Appolinario JC, Bueno JR, Coutinho W. Psychotropic drugs in the treatment of obesity. *CNS Drugs* 2004;18(10):629–51.

Attia 2005
Attia E, Wolk S, Cooper T, Glasofer D, Walsh TB. Plasma tryptophan during weight restoration in patient with anorexia nervosa. *Biological Psychiatry* 2005;57:674–8.

Bacaltchuk 2005
Bacaltchuk J, Hay P, Trefiglio R. Antidepressants versus psychological treatments and their combination for bulimia nervosa. In: *The Cochrane Library*, 2, 2005. Chichester: John Wiley & Sons, Ltd.

Baran 1995
Baran SA, Weltzin TE, Kaye WG. Low discharge weight and outcome in AN. *American Journal of Psychatry* 1995;152:1070–2.

Bosanac 2005
Bosanac P, Norman T, Burrows G, Beumont P. Serotonergic and dopaminergic systems in anorexia nervosa: a role for atypical antipsychotics?. *Australian and New Zealand Journal of Psychiatry* 2005;39: 146–53.

Braun 1994
Braun DL, Sunday SR, Halmi KA. Psychiatric comorbidity with eating disorders. *Psychological Medicine* 1994;24:859–67.

Bulik 2000
Bulik CM, Sullivan PF, Wade TD, Kendler KS. Twin studies of eating disorders: a review. *International Journal of Eating Disorders* 2000;27 (1):1–20.

Chamberlain 2005
Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neuroscience and Biobehavioral Review* 2005;29:399–419.

Chowdhury 2003
Chowdhury U, Gordon I, Lask B, Watkins B, Watt H, Christie D. Early onset anorexia nervosa: is there evidence of limbic system imbalance?. *International Journal of Eating Disorders* 2003;33:338.

Collier 1997
Collier DA, Arranxz MJ, Li T, Mupita D, Brown N, Treasure J. Association between 5-HT2A gene promoter polymorphism and anorexia nervosa. *Lancet* 1997;350:412.

Collier 2004
Collier D, Treasure JL. The aetiology of eating disorders. *British Journal of Psychiatry* 2004;185:363–5.

Connan 2003a
Connan F, Campbell IC, Katzman M, Lightman SL, Treasure J. A neurodevelopmental model for anorexia nervosa. *Physiology and Behaviour* 2003;79:13–24.

Connan 2003b
Connan F, Stanley S. Biology of apperite and weight regulation. In: Treasure J, Schmidt U & van Furth, E, editor(s). *Handbook of eating disorders*. 2nd Edition. Chichester: John Wiley and Sons, 2003:63–87.

Cowan 1996
Cowen PJ, Clifford EM, Walsh AE, Williams C, Fairburn CG. Moderate dieting causes 5-HT2C receptor supersensitivity. *Psychological Medicine* 1996;26:1155–9.

De Zwann 2003a
De Zwann M, Roerig J. Pharmacological treatment of eating disorders: a review. In: Maj M, Halmi K, Lopez-Ibor JJ, Sartorius N, editor(s). *Eating Disorders*. Chichester: John Wiley and Sons, 2003: 223 – 5.

de Zwann 2003b
de Zwann M. *Handbook of Eating Disorders*. Chichester: John Wiley and Sons, 2003.

DerSimonian 1986
DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;7(3):177–88.

Devlin 2002
Devlin B, Bacanu SA, Klump KL, Bulik CM, Fichter MM, Halmi KA, et al. Linkage analysis of anorexia nervosa incorporating behavioral covariates. *Human Molecular genetics* 2002;11:689–96.

Dickersin 1994
Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;309:1286–91.

Enoch 1998
Enoch MA, Kaye WH, Rotondo A, Greenberg BD, Murphy DL, Goldman D. 5-HT2A promoter polymorphism -1438G/A anorexia nervosa and obsessive -compulsive disorder. *Lancet* 1998;351:1785–6.

Fairburn 2005
Fairburn CG. Evidence-based treatment of anorexia nervosa. *International Journal of Eating Disorders* 2005;37:S26–30.

Favaro 2000
Favaro A, Caregaro L, Burlina AB, Santonastaso P. Tryptophan levels, excessive exercise, and nutritional status in anorexia nervosa. *Psychosomatic Medicine* 2000;62:535–8.

Fernstrom 1995
Fernstrom MH. Drugs that cause weight gain. *Obesity Research* 1995; 3 Suppl 4:435–9.

Fineberg 2004
Fineberg NA, Gale TM. Evidence-based pharmacotherapy of obsessive-compulsuve disorder. *International Journal of Neuropsychopharmacology* 2004;1:23.

Frank 2001b
Frank GK, Kaye WH, Weltzin TE, Perel J, Moss H, McConaha C, et al. Altered response to meta-chlorophenylpiperazine in anorexia nervosa: support for a persistent altereation of serotonin activity after short-term weight restoration. *International Journal of Eating Disorders* 2001;30:57–60.

Garfinkel 1996
Garfinkel PE, Lin E, Goering P, Spegg C, Goldbloom D, Kennedy S, et al. Should amenorrhoea be necessary for the diagnosis of anorexia nervosa? Evidence from a Canadian community sample. *British Journal of Psychiatry* 1996;168(4):500–6.

Geddes 2002
Geddes J, Butler R, Hatcher S. Depressive Disorders. *Clinical Evidence 84-106* 2002;7:84–106.

Gendall 1999
Gendall KA, Kaye WH, Altemus M, McConaha CW, La Via MC. Leptin, neuropeptide Y, and peptide YY in long-term recovered eating disorder patients. *Biological Psychiatry* 1999;46(2):292–9.

Gordon 1997
Gordon I, Lask B, Bryant-Waugh R, Christie D, Timimi S. Childhood onset anorexia nervosa - towards identifying a biological substrate. *International Journal of Eating Disorders* 1997;21(2):159–65.

Gorwood 1998
Gorwood P, Bouvard M, Mouren-Simeoni MC, Kipman A, Ades J. Genetics and anorexia nervosa: a review of candidate genes. *Psychiatric Genetics* 1998;8:1–12.

Graybiel 2005
Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. *Neuron* 2000;28:343–7.

Hay 2003
Hay P, Bacaltchuk J, Claudino A, Ben-Tovim D, Young PY. Individual psychotherapy in the outpatient treatment of adults with anorexia nervosa. In: *The Cochrane Library*, 4, 2003. Chichester: John Wiley & Sons, Ltd.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

Hsu 1986
Hsu LK. The treatment of anorexia nervosa. *American Journal of Psychiatry* 1986;143:573–81.

Jacobi 2004
Jacobi C, Hayward C, de Zwaan M, Kraemer HC, Agras WS. Coming to terms with risk factors for eating disorders: application of risk terminology and suggestions for a general taxonomy. *Psychological Bulletin* 2004;130(1):19–65.

Jimerson 1990
Jimerson DC, Lesem MD, Kaye WH. Eating disorders and depression: is there a serotonin connection?. *Biological Psychiatry* 1990;28: 443–54.

Katzman 2003
Katzman DK, Zipursky RB, Lambe EK, et al. A longitudinal magnetic resonance imaging study of brain changes in adolescents with AN. *Archives of Pediatric and Adolescent Medicine* 2003;151:793.

Kaye 1984
Kaye WH, Ebert MH, Raleigh M, Lake R. Abnormalities in CNS monoamine metabolism in anorexia nervosa. *Archives of General Psychiatry* 1984;41:350–5.

Kaye 1985
Kaye WH, Jimerson DC, Lake CR, Ebert MH. Altered norepinephrine metabolism following long-term weight recovery in patients with anorexia nervosa. *Psychiatry Research* 1985;14(4):333–42.

Kaye 1991a
Kaye WH, Gwirtsman HE, George DT, Ebert MH. Altered serotonin activity in anorexia nervosa after long-term weight restoration: Does elevated cerebrospinal fluid 5-hydroxyindoleacetic acid level correlate with rigid and obsessive behavior?. *Archives of General Psychiatry* 1991;48(6):556–62.

Kaye 1991c
Kaye WH, Weltzin TE. Serotonin activity in anorexia and bulimia nervosa. Relationship to the modulation of feeding and mood. *Journal of Clinical Psychiatry* 1991;52 Suppl:41–8.

Kaye 1998
Kaye W, Gendall K, Strober M. Serotonin Neuronal Function and Selective Serotonin and Selective Serotonin Reuptake Inhibitor Treatment in Anorexia and Bulimia Nervosa. *Biological Psychiatry* 1998; 44(9):825–38.

Kaye 1999a
Kaye WH, Frank GK, McConaha C. Altered dopamine activity after recovery from restricting-type anorexia nervosa. *Neuropsychopharmacology* 1999;21(4):503–6.

Kaye 1999b
Kaye W, Strober M, Stein D, Gendall K. New directions in treatment research of anorexia and bulimia nervosa. *Biological Psychiatry* 1999; 45:1285–92.

Kaye 2001a
Kaye WH, Frank GK, Meltzer CC, et al. Apllication of a latent class analysis to empirically define eating disorder phenotypes. *American Journal of Psychiatry* 2001;158:1152–5.

Kaye 2003
Kaye WH, Barbarich NC, Putnam K, Gendall KA, Fernstrom J, Fernstrom M, et al. Anxiolytic effects of acute tryptophan depletion in anorexia nervosa. *International Journal of Eating Disorders* 2003; 33:257–67.

Klump 2001
Klump KL, Miller KB, Keel PK, McGue M, Iacono WG. Genetic and environmental influences on anorexia nervosa syndromes in a population-based twin sample. *Psychological Medicine* 2001;31(4): 737–40.

Kortegaard 2001
Kortegaard LS, Hoerder K, Joergensen J, Gillberg C, Kyvik KO. A preliminary population-based twin study of self-reported eating disorder. *Psychological Medicine* 2001;31(2):361–5.

Lask 2005
Lask B, Gordon I, Christie D, Frampton I, Chowdhury U, Watkins B. Functional neuroimaging in early-onset anorexia nervosa. *International Journal of Eating Disorders* 2005;37:S49–S51.

Leibowitz 1986
Leibowitz SF, Shor-Posner G, Weiss GF. Brain serotonin and eating behavior. *Appetite* 1986;7 Suppl:1–14.

Licinio 2005
Licinio J, Wong ML. Depression, antidepressants and suicidality: a critical appraisal. *Nature Reviews. Drug Discovery* 2005;4(2):165–71.

Lilenfeld 1998
Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnicov K, Pollice C, et al. A controlled family study of anorexia nervosa and bulimia nervosa:psychiatric disorders in first-degree relatives and effects of proband comorbidity. *Archives of General Psychiatry* 1998; 55:603–10.

Lucas 1991
Lucas AR, Beard CM, O'Fallon WM, Kurland LT. 50-year trends in the incidence of anorexia nervosa in Rochester, Minnesota: A population based study. *American Journal of Psychiatry* 1991;148:917–22.

Mantzoros 1997
Mantzoros C, Flier JS, Lesem MD, Brewerton TD, Jimerson DC. Cerebrospinal fluid leptin in anorexia nervosa: correlation with nutritional status and potential role in resistance to weight gain. *Journal of Clinical Endocrinology and Metabolism* 1997;82(6):1845–51.

Mayer 1998
Mayer LE, Walsh BT. Pharmacotherapy of eating disorders. In: Hoek HW, Treasure JL, Katzman MA, editor(s). *Neurobiology in the treatment of eating disorders*. Chichester: Wiley, 1998:383–405.

Moncrieff 2001
Moncrieff J, Churchill R, Colin Drummond D, McGuire H. Development of quality assessment instrument for trials of treatments for depression and neurosis. *International Journal of Methods in Psychiatric Research* 2001;10(3):126–33.

Morgan 1975
Morgan, HG, Russell, GF. Value of family background and clinical features as predictors of longterm outcome in anorexia nervosa: Four year follow-up study of 41 patients. *Psychological Medicine* 1975;5: 355–71.

Morgan 1988
Morgan HG, Hayward AE. Clinical assessment of anorexia nervosa. The Morgan-Russell assessment schedule. *British Journal of Psychiatry* 1988;152:367–71.

Mulrow 1999
Mulrow CD, Oxman AD (eds). *Cochrane Collaboration Handbook*. London: BMJ Publishing Group, 1999.

Nasser 2000
Nasser M, Katzman M, Gordon R. *Cultures in transition: eating disorders as a global marker*. London: Brunner, Routledge, 2000.

NCCMH 2004
National Collaborating Centre for Mental Health. *Eating disorders: core interventions in the treatment and management fo anorexia nervosa, bulimia nervosa and related eating disorders*. London: British Psychological Society and Royal College of Psychiatrists, 2004.

Nielsen 1998
Nielsen S, Moller-Madsen S, Isager T, Jorgensen J, Pagsberg K, Theander S. Standardized mortality in eating disorders-a quantitative summary of previously published and new evidence. *Journal of Psychosomatic Research* 1998;44:413–34.

Palmer 2000
Palmer RL. *Management of Eating Disorders*. Chichester: John Wiley & Sons, 2000.

Pawluck 1998
Pawluck DE, Gorey KM. Secular trends in the incidence of anorexia nervosa: Integrative review of population-based studies. *International Journal of Eating Disorders* 1998;23:347–52.

Pinel 2000
Pinel JPJ, Assanand S, Lehman DR. Hunger, eating, and ill health. *American Psychology* 2000;55(10):1105–16.

Pirke 1996
Pirke KM. Central and peripheral noradrenalin regulation in eating disorders. *Psychiatry Research* 1996;62:43–9.

PRCG 2001
Price Foundation Collaborative Group. Deriving behavioural phenotypes in an international multi-centre study of eating disorders. *Psychological Medicine* 2001;31:635–45.

Reilly 2000
Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000;355:1048–52.

Ribases 2004
Ribases M, Gratacos M, Fernandez-Aranda F, Bellodi L, Boni C, Anderluh M, et al. Association of BDNF with anorexia, bulimia, age of onset of weight loss in six European populations. *Human Molecular Genetics* 2004;13(12):1205–12.

Schmidt 2003
Schmidt U. Aetiology of eating disorders in the 21st century. New answers to old questions. *European Child and Adolescent Psychiatry* 2003;12 Suppl 1:30–7.

Soomro 2002
Soomro GM. Obsessive Compulsive Disorder. *Clinical Evidence* 2002;7:124–34.

Stallone 1989
Stallone D, Nicolaidis S, Gibbs J Stallone D, Nicolaidis S, Gibbs J. Cholecystokinin-induced anorexia depends on serotoninergic function. *American Journal of Physiology* 1989;256(5Pt2):1138–41.

Steiger 2004
Steiger H. Eating disorders and the serotonin connection: state, trait and developmental effects. *Journal of Psychiatry and Neuroscience* 2004;29:20.

Steinhausen 2002
Steinhausen HC. The outcome of anorexia nervosa in the 20th century. *American Journal of Psychiatry* 2002;159:1284–93.

Stice 2002
Stice E. Risk and maintenance factors for eating pathology: a meta-analytic review. *Psychological Bulletin* 2002;128:825–48.

Strober 1997b
Strober M, Freeman R, Morrell W. The long-term course of severe anorexia nervosa in adolescents:survival analysis of recovery, relapse, and outcome predictors over 10-15 years in a prospective study. *International Journal of Eating Disorders* 1997;22:339–60.

Strober 2000
Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndromes. *American Journal of Psychiatry* 2000;157(3):393–401.

Sullivan 1995
Sullivan PF. Mortality in anorexia nervosa. *American Journal of Psychiatry* 1995;152:1073–4.

Treasure 2004
Treasure J, Schmidt U. Anorexia nervosa. *Clinical Evidence* 2004;12: 1294–305.

Vaswani 2004
Vaswani M, Karla H. Selective serotonin re-uptake inhibitors in anorexia nervosa. *Expert Opinion Investigational Drugs* 2004;13(4): 349–57.

Verhulst 1997
Verhulst FC, van der Ende J, Ferdinand RF, Kasius M. The prevalence of DSM-III-R diagnoses in a national sample of Dutch adolescents. *Archives of General Psychiatry* 1997;54:329–36.

Wade 2000
Wade TD, Bulik CM, Neale M, Kendler KS. Anorexia nervosa and major depression: shared genetic and environmental risk factors. *American Journal of Psychiatry* 2000;157(3):469–71.

WHO 1992
World Health Organization. *The ICD-10 Classification of Mental and Behavior Disorders*. 10 Edition. Geneva: World Health Organization, 1992.

Wiseman 1998
Wiseman CV, Harris WA, Halmi KA. Eating disorders. *Medical Clinics of North America* 1998;82(1):145–59.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Attia 1998
Methods	RCT; placebo controlled; double-blind; duration variable: maximum 7 weeks or until reached 90% of ideal body weight plus one week (approximately 5 to 6 weeks); plasma levels of drug measured at week 4 and end of treatment; It is not certain that ITT analysis was conducted: of 33 patients initially randomised, data from only 31 were considered for analysis.
Participants	AN Diagnosis: DSM-IV (criteria A, B and C) and weight less then 80% of ideal body weight ; 31 female inpatients: 12 AN-restrictive and 19 AN-binge/purge; significant difference in mean age between groups: fluoxetine 29.1ys (SD=7.2) and placebo 23.4 ys (SD=6.4).
Interventions	Fluoxetine 60 mg (mean dose 56mg/d SD=11.2) X placebo; all patients also attended individual psychotherapy (supportive and cognitive-behav), group sessions, family sessions (if available) and a structured behavioral treatment aimed at normalizing eating behavior and weight.
Outcomes	Weight gain: end of treatment mean percent of ideal body weight, mean change in percent of ideal body weight per day; improvement in eating disorders symptoms (Anorexic Behvaior Scale, BSQ, EAT, Y-Brown-Cornell Eating Disorder Scale); improvement in depression and obsessive-compulsive symptoms (mean scores of SCL-90)

	and clinical improvement (mean scores in CGI); proportion of drop-outs for any reason and for side effects reported per group, and number of subjects reporting side effects also.
Notes	Allocation concealment not mentioned; although groups differed in mean age, age was not related to clinical outcome on any clinical outcome measure; mean duration of treatment not different between groups (fluoxetine = 36.1 days SD 14.1 and placebo = 37.4 days SD 13.8); self -report data from one patient not analyzed (unreliable).
Allocation concealment	B

Study	Biederman 1985
Methods	RCT; placebo controlled; double-blind; multi-centre (2); 3 arms (parallel); amitriptiline x placebo x control group (no drug); 5 weeks duration; compliance assessed (plasma levels measured weekly); ITT analysis apparently not realized (some outcomes do not consider all patients).
Participants	AN Diagnosis: Feighner + DSMIII criteria; 25 in and outpatients; amitriptyline n=11, mean age 18.4ys (SD=4.9); placebo n=14, 17.2ys (SD=4.3); gender not specified, nor anorexia type.
Interventions	Amitriptyline (mean daily dose 115 mg SD= 31) X placebo; all patients received medical and psychiatric treatment including suportive measures, nutritional counseling, individual psychotherapy and family intervention. Inpatients also received Behavior Modification Programme.
Outcomes	Weight gain: mean weekly weight gain (kg/week) and number of patients responding to categories of percentage of weight gain; improvement in eating disorders, depression, anxiety, and obsessive-compulsive symptoms, and global clinical effect measured by weekly changes in scores in scales (EAT-40,SADS-C, HSCL, Global Severity and Global Improvement Scales); outcomes in overall symptomatology offered through number of patients per categories of percentages of response. Drop-outs not informed (apparently none as total number of patients were evaluated in some outcomes); number of patients reporting specific side-effects in each group referred but total number of patients with adverse events not described.
Notes	Allocation concealment not mentioned; drug plasma levels available for 8 patients showed wide variation at the same dose (2 at the lower limit of assay sensitivity suggesting compliance problems); high refusal rate to study: 18 patients, who formed a control (no drug) group, not considered in this review.
Allocation concealment	B

Study	Brambilla 1995a
Methods	RCT; two arms (not placebo controlled); open study; one center; 4 months duration; although authors informed that ITT analysis were not performed, they also informed that there were no drop-outs.
Participants	AN - Restrictive Type Diagnosis: DSMIII-R + IV criteria; 22 female outpatients: nortriptyline n=7, fluoxetine n=15; overall sample mean age was 21 years (SD=5); groups comparable in BMI (no information on demographic and clinical factors comparisons).
Interventions	Nortriptyline 75mg/d X fluoxetine 60mg/d; all patients also attended CBT and nutritional therapy sessions.
Outcomes	Weight gain: evaluated through BMI; evaluation of eating disorders symptomatology (EDI and BITE), depression and anxiety symptomatology (HRS-D and HRS-A) .
Notes	Allocation concealment based on use of sealed opaque envelopes; assesment of compliance only based in family support (no plasma levels of drug); no drop-outs. Information provided by first author.

Characteristics of included studies (*Continued*)

Allocation concealment	A

Study	Brambilla 1995b
Methods	RCT; two arms (not placebo controlled); open study; one center; 4 months duration ; although authors informed that ITT analysis were not performed, they also informed that there were no drop-outs.
Participants	AN- Binge-Eating / Purging Type Diagnosis: DSMIII-R + IV criteria ; 13 female outpatients: amineptine n=7, fluoxetine n=6; overall sample mean age was 23.1 (SD=6.8); groups comparable in BMI (no information on clinical factors comparisons).
Interventions	Amineptine 300mg/d X fluoxetine 60mg/d; all patients also attended CBT and nutritional therapy sessions.
Outcomes	Weight gain: evaluated through BMI; evaluation of eating disorders symptomatology (EDI and BITE), depression and anxiety symptomatology (HRS-D and HRS-A) .
Notes	Allocation concealment based on use of sealed opaque envelopes; assesment of compliance only based in family support (no plasma levels of drug); no drop-outs. Information provided by first author.
Allocation concealment	A

Study	Halmi 1986
Methods	RCT; placebo controlled; double-blind; duration variable (until reached target weight or maximum of 90 days) but mean duration was 4 to 5 weeks; multi-centre (2); 3 arms (parallel) (amitriptiline x cyproheptadine x placebo); ITT analysis not specifically reported and different number of patients were evaluated in outcomes.
Participants	AN Diagnosis: DSM III + amenorrhea; 48 female inpatients (72 randomised considering cyproheptadine group) with 33 bulimic type and 39 restrictors; amitriptyline n=23 and placebo n=25; Overall mean age was 20.56ys SD=5.1. No information on comparability of groups.
Interventions	Amitriptyline (maximum dose 160mg) X placebo, added to inpatient interventions not specified, except for a refeeding programme.
Outcomes	Weight gain: number of patients achieving target weight (within 5% of normal range), average daily weight gain (kg/day) and time to achieve target weight (in those who achieved it); improvement in eating disorders symptoms (Anorectic Behavior Scale, and Anorectic Atittude Scale); improvement in depression (HRS-D, HSCL-90, BDI); drop-outs for any reason (treatment failures) and for side-effects stated.
Notes	Allocation concealment not mentioned. No reference to measurement of drug plasma levels; statistical significant difference (greater achievement of target weight) in patients using maximum dose; placebo group presented a drop-out rate of 36%.
Allocation concealment	B

Study	Lacey 1980
Methods	RCT; placebo controlled; double-blind;

Characteristics of included studies (*Continued*)

	duration variable: drug treatment until reached target weight (around 10-11 weeks); follow-up at one year and four years after weight gain; ITT analysis not clear (withdrawals were followed up and seems to have been included in analyses).
Participants	AN Diagnosis: criteria not described, authors refer to consecutive admissions to anorectic unit at hospital; 16 female inpatients: clomipramine n=8, mean age 20.9 yrs and placebo n=8, mean age 21.4 yrs (no SD informed); groups comparable (sex,age, weight, clinical history and social class). 7 AN-Restrictive and 1AN-Bulimic -type patient in each group.
Interventions	Clomipramine 50mg X placebo added to inpatient refeeding behavioural programme (bed-rest + planned meal), and individual and family psychotherapies; outpatient follow-up monitored weight and related behaviour coupled with psychotherapy (no drug).
Outcomes	Weight gain: absolute mean weight gain (kg) , mean daily rate of weight gain (kg/day), mean number of days to achieve target weight and mean % of ideal weight at one year follow-up; aspects of mood (sadness, anxiety, irritability) and appetite behaviour measured through analogue scales (developed by authors); drop -outs for any reason and for side-effects stated.
Notes	Allocation concealment not mentioned. Low dose of clomipramine used; no reference to assessment of compliance (drug levels); number of evaluated patients not stated for some outcome measures (data probably refers to the complete sample as authors inform that all patients reached target weight (including drop-outs) and offer data of 1-year follow-up.
Allocation concealment	B

Study	**Ruggiero 2001**
Methods	RCT; 3 arms (not placebo controlled); single-blind (outcome assessor); three months duration; ITT analysis not clear (number of before and post - randomisation exclusions not clearly informed and outcomes refers to 35 patients who finished the re-feeding phase).
Participants	AN Restrictive Type Diagnosis: DSM-IV criteria; 35 inpatients (gender not specified): clomipramine n= 13, mean age 23.69 (SD 4.57); fluoxetine n=10, mean age 24.50 (SD 5.06) ; groups comparable in age and weight, but no information in other clinical or demographic aspects).
Interventions	Clomipramine mean daily dose 57.69 mg SD = 25.79; fluoxetine mean daily dose 28.00mg SD = 10.32; all patients received a nutritional and psychoeducation-al treatment.
Outcomes	Weight gain: end of treatment mean weight and percentual of weight increase; improvement in eating disorders symptoms evaluated through Eating Disorder Interview based on Long Interval Follow-up (LIFE II BEI).
Notes	Allocation concealment not mentioned; data from one of the arms (amisulpride) was not considered: no reference to assesment of compliance (drug blood measurement); drop-outs not referred.
Allocation concealment	B

Characteristics of excluded studies

Barbarich 2004	RCT of additional nutritional supplements to potentiate the effects of fluoxetine in underweight AN subjects, which was not pertinent to the questions in this review
Bergh 1996	Retrospective observational study (clinical records) of citalopram in AN, which was not pertinent to the questions in this review

Characteristics of excluded studies (*Continued*)

Bergh 2002	RCT of training of eating behavior and society by computer support, reduction of physical hyperactivity, supply or warmth and restoration of social function in eating disorders patients, which was not pertinent to the questions in this review
Birmingham 1994	RCT of zinc treatment AN, which was not pertinent to the questions in this review
Brambilla 1995c	RCT of T-lymphocite cholecystokinin-8 and beta-endorphin concentrations in AN patients, which was not pertinent to the questions in this review
Calandra 1999	Uncontrolled open trial of citalopram in eating disorders patients,which was not pertinent to the questions in this review
Corwin 1995	Retrospective observational study (chart review) of TCA versus fluoxetine in AN, which was not pertinent to the questions in this review
Eckert 1987	RCT investigates psychological aspects of subgroups of AN patients participating in a drug treatment, which was not pertinent to the questions in this review
Falk 1985	RCT investigates activity measures of AN patients in a drug treatment, which was not pertinent to the questions in this review
Fassino 2002	RCT of citalopram for AN compared to no-drug controls, which was not pertinent to the questions in this review
Ferguson 1987	Single-case report of AN treated with fluoxetine, which was not pertinent to the questions in this review
Ferguson 1999	Retrospective observational study (chart review) of SSRI versus no drug group AN patients, which was not pertinent to the questions in this review
Frank 2001a	Case reports of sertraline in underweight binge/eating purging type eating disorders, which was not pertinent to the questions in this review
Gross 1981	RCT of litium carbonate for AN, which was not pertinent to the questions in this review
Gwirtsman 1990	Uncontrolled open clinical trial of fluoxetine in AN, which was not pertinent to the questions in this review
Halmi 1982	RCT of cyproheptadine and amitriptyline for AN (partial data of included study: Halmi et al, 1986)
Halmi 1983	RCT of cyproheptadine and amitriptyline for AN (partial data of included study: Halmi et al, 1986)
Halmi 1999	RCT of fluoxetine versus CBT for relapse prevention of AN (ongoing trial - abstract published in APA Conference Annals), which was not pertinent to the questions in this review
Holtkamp 2005	Retrospective observational study (chart review) of SSRIs versus no drug treatment of child and adolescent AN, which was not pertinent to the questions in this review
Hudson 1985	Open clinical trial, not randomized, of drug treatment (AD, litium carbonate, carbamazepine) in AN patients, which was not pertinent to the questions in this review
Kaye 1991b	Open label clinical trial of fluoxetine for relapse prevention of AN, which was not pertinent to the questions in this review
Kaye 2001b	RCT of fluoxetine for relapse prevention of AN, which was not pertinent to the questions in this review
Moore 1977	Case report of amitriptyline in AN patient, which was not pertinent to the questions in this review
Mumford 1984	Single-case study of interaction of imipramine and CBT in the treatment of AN,which was not pertinent to the questions in this review
Pallanti 1997	Uncontrolled open trial of citalopram in AN, which was not pertinent to the questions in this review
Ricca 1999	Quasi-randomised study of venlafaxine versus fluoxetine in atypical anorectic patients, which was not pertinent to the questions in this review
Ruggiero 2003	Not-randomised, open controlled trial of nutritional management with and without fluoxetine in AN, which was not pertinent to the questions in this review
Sanchez 1993	Uncontrolled, open trial of fluvoxamine in AN patients, which was not pertinent to the questions in this review
Santonastaso 2001	Not randomised, open controlled trial of sertraline versus a no-drug group of AN patients, which was not pertinent to the questions in this review

Characteristics of excluded studies (*Continued*)

Strobel 2004	Retrospective observational study (clinical reports) of paroxetine versus clomipramine for AN (abstract information), which was not pertinent to the questions in this review
Strober 1997a	Naturalistic prospective longitudinal follow-up study of relapse prevention for AN (matched historical controls), which was not pertinent to the questions in this review
Strober 1999	Open label clinical trial of adjunctive fluoxetine for AN compared to matched historical controls, which was not pertinent to the questions in this review
Vandereycken 1984	RCT of neuroleptic treatment, which was not pertinent to the questions in this review

ANALYSES

Comparison 01. ANTIDEPRESSANTS VS. PLACEBO

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean weight gain (kg) (high is better)			Standardised Mean Difference (Random) 95% CI	Totals not selected
02 Mean percentage of target weight at 1y. follow-up (high is better)			Standardised Mean Difference (Random) 95% CI	Totals not selected
03 End of treatment mean percentage of ideal body weight (high is better)			Standardised Mean Difference (Random) 95% CI	Totals not selected
04 Number of patients not achieving target weight	2	79	Relative Risk (Random) 95% CI	0.83 [0.41, 1.67]
05 Rate of weight gain (kg/day) (high is better)			Standardised Mean Difference (Random) 95% CI	Totals not selected
06 Rate of weight gain (change in % of ideal body weight /day) (high is better)			Standardised Mean Difference (Random) 95% CI	Totals not selected
07 Time to achieve target weight (days)			Standardised Mean Difference (Random) 95% CI	Totals not selected
08 Absence of greater than 30% increase in weight (weight gain of 30% or less)			Relative Risk (Random) 95% CI	Totals not selected
09 End-point mean scores in Eating Disorder Scales			Standardised Mean Difference (Random) 95% CI	Totals not selected
10 Absence of greater than 50% response in antidepressant effect (50% response or less in SADS-C)			Relative Risk (Random) 95% CI	Totals not selected
11 End-point mean scores in Depression Scales			Standardised Mean Difference (Random) 95% CI	Subtotals only
12 Absence of greater than 50% response in antiobsessional effect (50% response or less in HSCL)			Relative Risk (Random) 95% CI	Totals not selected
13 End-point mean scores in Obsessive Subscale (SCL-90)			Standardised Mean Difference (Random) 95% CI	Totals not selected

14 Absence of greater than 50% response in antianxiety effect (50% response or less in SADS-C)	Relative Risk (Random) 95% CI	Totals not selected
15 Absence of greater than 50% response in clinical global effect (50% response or less in G. Improv. Scale)	Relative Risk (Random) 95% CI	Totals not selected
16 End-point mean scores in clinical global improvement scale (CGI)	Standardised Mean Difference (Random) 95% CI	Totals not selected
17 Rates of non-completers	Relative Risk (Random) 95% CI	Subtotals only
18 Number of patients reporting side effects	Relative Risk (Random) 95% CI	Subtotals only

Comparison 02. ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 End of treatment mean BMI (high is better)			Standardised Mean Difference (Random) 95% CI	Subtotals only
02 End of treatment mean absolute weight (high is better)			Standardised Mean Difference (Random) 95% CI	Totals not selected
03 Mean percentage of weight increase (high is better)			Standardised Mean Difference (Random) 95% CI	Totals not selected
04 End-point mean scores in Eating Disorders Inventory (EDI)			Standardised Mean Difference (Random) 95% CI	Subtotals only
05 End-point mean scores in Hamilton Depression Scale (HRS-D)			Standardised Mean Difference (Random) 95% CI	Subtotals only
06 End-point mean scores in Hamilton Anxiety Scale (HRS-A)			Standardised Mean Difference (Random) 95% CI	Subtotals only

COVER SHEET

Title	Antidepressants for anorexia nervosa
Authors	Claudino AM, Hay P, Lima MS, Bacaltchuk J, Schmidt U, Treasure J
Contribution of author(s)	AMC - protocol writing, data searches, quality assessment, data extraction and entering, review writting MSL - protocol writing, quality checking of data extraction and entering, statistical advice and commentary on findings and conclusions JB - - protocol writing, quality assessment and data extraction, commentary on findings and conclusions PH - protocol and revision commentaries JT - protocol and revision commentaries US - protocol and revision commentaries
Issue protocol first published	2003/2
Review first published	2006/1

Date of most recent amendment	14 November 2005
Date of most recent SUBSTANTIVE amendment	04 November 2005
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Angélica Claudino Eating Disorders Program Department of Psychiatry Federal University of São Paulo - UNIFESP / Escola Paulista de Me Rua dos Otonis 887 São Paulo SP CEP 04025 002 BRAZIL E-mail: angelica@psiquiatria.epm.br Tel: 55 11 55791543 Fax: 55 11 30799232
DOI	10.1002/14651858.CD004365.pub2
Cochrane Library number	CD004365
Editorial group	Cochrane Depression, Anxiety and Neurosis Group
Editorial group code	HM-DEPRESSN

GRAPHS AND OTHER TABLES

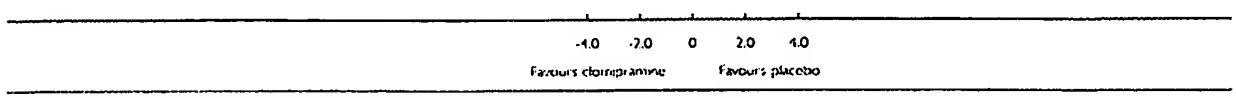
Analysis 01.01. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 01 Mean weight gain (kg) (high is better)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 01 Mean weight gain (kg) (high is better)

Study	placebo N	placebo Mean(SD)	clomipramine N	clomipramine Mean(SD)	Standardised Mean Difference (Random) 95% CI	Standardised Mean Difference (Random) 95% CI
Lacey 1980	8	14.70 (4.60)	8	11.33 (5.32)		0.64 [-0.37, 1.65]



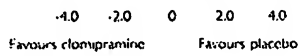
Analysis 01.02. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 02 Mean percentage of target weight at 1y. follow-up (high is better)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 02 Mean percentage of target weight at 1y. follow-up (high is better)

Study	placebo		clomipramine		Standardised Mean Difference (Random)	Standardised Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Lacey 1980	8	89.89 (8.38)	8	95.63 (6.04)		-0.74 [-1.77, 0.28]



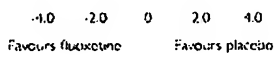
Analysis 01.03. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 03 End of treatment mean percentage of ideal body weight (high is better)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 03 End of treatment mean percentage of ideal body weight (high is better)

Study	placebo		fluoxetine		Standardised Mean Difference (Random)	Standardised Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Attia 1998	16	87.40 (4.70)	15	86.60 (6.30)		0.14 [-0.56, 0.85]



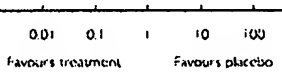
Analysis 01.04. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 04 Number of patients not achieving target weight

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 04 Number of patients not achieving target weight

Study	treatment	placebo	Relative Risk (Random)	Weight	Relative Risk (Random)
	n/N	n/N	95% CI	(%)	95% CI
Attia 1998	4/15	4/16		34.4	1.07 [0.32, 3.52]
Halmi 1986	6/23	9/25		65.6	0.72 [0.31, 1.72]
Total (95% CI)	38	41		100.0	0.83 [0.41, 1.67]
Total events: 10 (treatment), 13 (placebo)					
Test for heterogeneity chi-square=0.26 df=1 p=0.61 I² =0.0%					
Test for overall effect z=0.53 p=0.6					



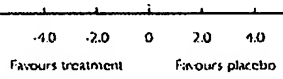
Analysis 01.05. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 05 Rate of weight gain (kg/day) (high is better)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 05 Rate of weight gain (kg/day) (high is better)

Study	placebo		treatment		Standardised Mean Difference (Random)	Standardised Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Haimi 1986	16	0.23 (0.12)	17	0.31 (0.17)		-0.53 [-1.22, 0.17]
Lacey 1980	8	0.21 (0.03)	8	0.17 (0.04)		1.07 [0.00, 2.14]



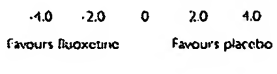
Analysis 01.06. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 06 Rate of weight gain (change in % of ideal body weight /day) (high is better)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 06 Rate of weight gain (change in % of ideal body weight /day) (high is better)

Study	placebo		fluoxetine		Standardised Mean Difference (Random)	Standardised Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Attia 1998	16	0.42 (0.11)	15	0.35 (0.17)		0.48 [-0.24, 1.20]



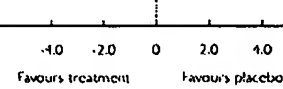
Analysis 01.07. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 07 Time to achieve target weight (days)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 07 Time to achieve target weight (days)

Study	treatment		placebo		Standardised Mean Difference (Random)	Standardised Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Haimi 1986	17	32.24 (17.37)	16	45.00 (18.34)		-0.70 [-1.40, 0.01]
Lacey 1980	8	76.00 (24.00)	8	72.00 (28.00)		0.15 [-0.84, 1.13]

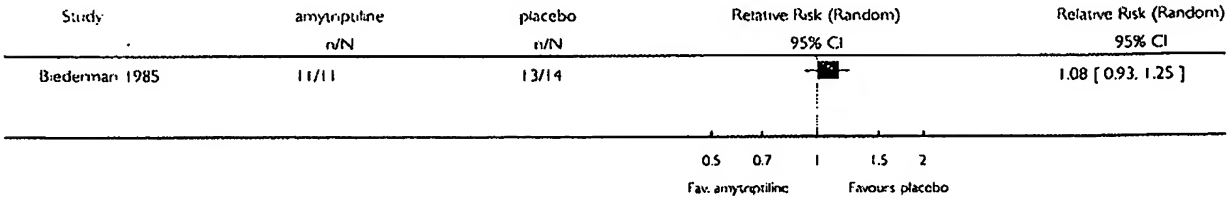


Analysis 01.08. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 08 Absence of greater than 30% increase in weight (weight gain of 30% or less)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 08 Absence of greater than 30% increase in weight (weight gain of 30% or less)

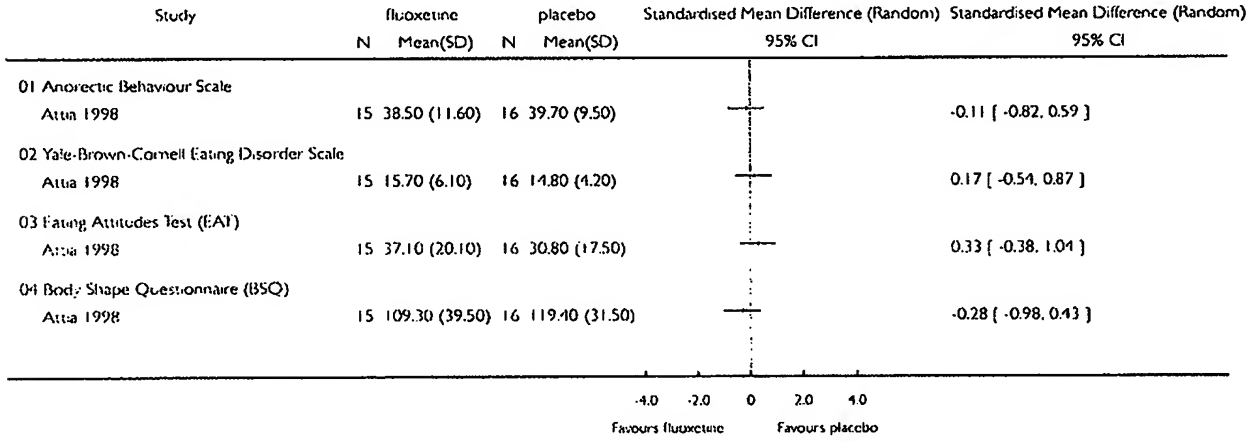


Analysis 01.09. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 09 End-point mean scores in Eating Disorder Scales

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 09 End-point mean scores in Eating Disorder Scales



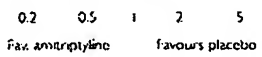
Analysis 01.10. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 10 Absence of greater than 50% response in antidepressant effect (50% response or less in SADS-C)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 10 Absence of greater than 50% response in antidepressant effect (50% response or less in SADS-C)

Study	amitriptyline n/N	placebo n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
Biederman 1985	11/11	11/14		1.27 [0.97, 1.67]



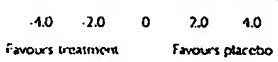
Analysis 01.11. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 11 End-point mean scores in Depression Scales

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 11 End-point mean scores in Depression Scales

Study	treatment N	Mean(SD)	placebo N	Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 Beck Depression Scale							
Attia 1998	15	15.00 (11.30)	16	14.00 (8.90)		39.2	0.10 [-0.61, 0.80]
Haimi 1986	23	13.10 (12.10)	25	13.60 (9.80)		60.8	-0.04 [-0.61, 0.52]
Subtotal (95% CI)	38		41			100.0	0.01 [-0.43, 0.45]
Test for heterogeneity chi-square=0.09 df=1 p=0.76 I² =0.0%							
Test for overall effect z=0.05 p=1							
02 SCL-90 Depression Subscale							
Attia 1998	15	2.30 (1.00)	16	2.20 (0.80)		100.0	0.11 [-0.60, 0.81]
Subtotal (95% CI)	15		16			100.0	0.11 [-0.60, 0.81]
Test for heterogeneity: not applicable							
Test for overall effect z=0.30 p=0.8							
03 Hamilton Depression Scale							
Haimi 1986	16	14.10 (6.90)	20	17.70 (8.50)		100.0	-0.45 [-1.12, 0.22]
Subtotal (95% CI)	16		20			100.0	-0.45 [-1.12, 0.22]
Test for heterogeneity: not applicable							
Test for overall effect z=1.32 p=0.2							



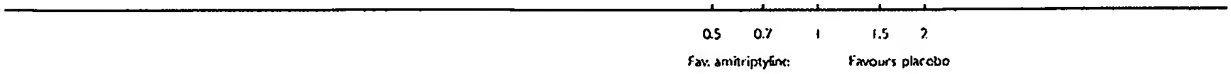
Analysis 01.12. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 12 Absence of greater than 50% response in antiobsessional effect (50% response or less in HSCL)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 12 Absence of greater than 50% response in antiobsessional effect (50% response or less in HSCL)

Study	amytriptyline n/N	placebo n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
Biederman 1985	11/11	13/14		1.08 [0.93, 1.25]



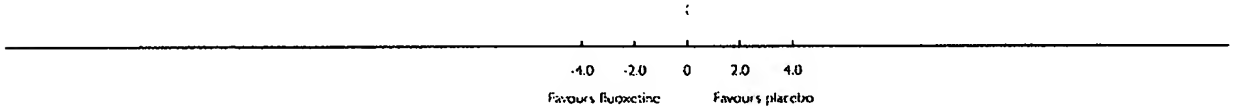
Analysis 01.13. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 13 End-point mean scores in Obsessive Subscale (SCL-90)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 13 End-point mean scores in Obsessive Subscale (SCL-90)

Study	fluoxetine N	fluoxetine Mean(SD)	placebo N	placebo Mean(SD)	Standardised Mean Difference (Random) 95% CI	Standardised Mean Difference (Random) 95% CI
Attia 1998	15	1.90 (1.00)	16	1.70 (0.50)		0.25 [-0.46, 0.96]



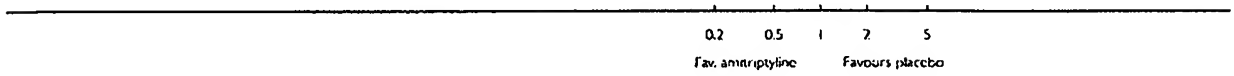
Analysis 01.14. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 14 Absence of greater than 50% response in antianxiety effect (50% response or less in SADS-C)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 14 Absence of greater than 50% response in antianxiety effect (50% response or less in SADS-C)

Study	amitriptyline n/N	placebo n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
Biederman 1985	11/11	12/14		1.17 [0.94, 1.44]



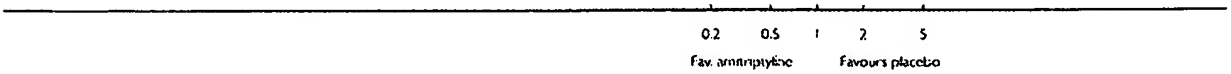
Analysis 01.15. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 15 Absence of greater than 50% response in clinical global effect (50% response or less in G. Improv. Scale)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 15 Absence of greater than 50% response in clinical global effect (50% response or less in G. Improv. Scale)

Study	amitriptyline	placebo	Relative Risk (Random)	Relative Risk (Random)
	n/N	n/N	95% CI	95% CI
Biederman 1985	10/11	13/14		0.98 [0.77, 1.24]



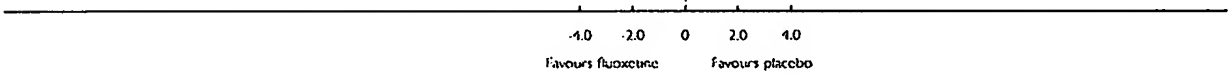
Analysis 01.16. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 16 End-point mean scores in clinical global improvement scale (CGI)

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 16 End-point mean scores in clinical global improvement scale (CGI)

Study	fluoxetine		placebo		Standardised Mean Difference (Random)	Standardised Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Attia 1998	15	2.50 (1.40)	16	2.80 (1.50)		-0.20 [-0.91, 0.51]



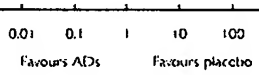
Analysis 01.17. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 17 Rates of non-completers

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 17 Rates of non-completers

Study	ADs n/N	placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 for any reason					
Attia 1998	4/15	4/16		31.2	1.07 [0.32, 3.52]
* Biederman 1985	0/11	0/14		0.0	Not estimable
Halmi 1986	6/23	9/25		59.5	0.72 [0.31, 1.72]
Lacey 1980	2/8	1/8		9.3	2.00 [0.22, 17.89]
Subtotal (95% CI)	57	63		100.0	0.90 [0.46, 1.75]
Total events: 12 (ADs), 14 (placebo)					
Test for heterogeneity chi-square=0.83 df=2 p=0.66 I² =0.0%					
Test for overall effect z=0.32 p=0.8					
02 drop-outs for side effects					
Attia 1998	0/15	1/16		40.7	0.35 [0.02, 8.08]
* Biederman 1985	0/11	0/14		0.0	Not estimable
* Halmi 1986	0/23	0/25		0.0	Not estimable
Lacey 1980	1/8	1/8		59.3	1.00 [0.07, 13.37]
Subtotal (95% CI)	57	63		100.0	0.66 [0.09, 4.82]
Total events: 1 (ADs), 2 (placebo)					
Test for heterogeneity chi-square=0.25 df=1 p=0.61 I² =0.0%					
Test for overall effect z=0.42 p=0.7					



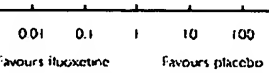
Analysis 01.18. Comparison 01 ANTIDEPRESSANTS VS. PLACEBO, Outcome 18 Number of patients reporting side effects

Review: Antidepressants for anorexia nervosa

Comparison: 01 ANTIDEPRESSANTS VS. PLACEBO

Outcome: 18 Number of patients reporting side effects

Study	fluoxetine n/N	placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Attia 1998	2/15	1/16		100.0	2.13 [0.22, 21.17]
Subtotal (95% CI)	15	16		100.0	2.13 [0.22, 21.17]
Total events: 2 (fluoxetine), 1 (placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.65 p=0.5					



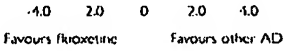
Analysis 02.01. Comparison 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 01 End of treatment mean BMI (high is better)

Review: Antidepressants for anorexia nervosa

Comparison: 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 01 End of treatment mean BMI (high is better)

Study	other AD N	other AD Mean(SD)	fluoxetine N	fluoxetine Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 fluoxetine versus nortriptyline							
Brambilla 1995a	7	18.30 (1.70)	15	16.30 (2.60)		100.0	0.81 [-0.12, 1.75]
Subtotal (95% CI)	7		15			100.0	0.81 [-0.12, 1.75]
Test for heterogeneity: not applicable							
Test for overall effect: z=1.70 p=0.09							
02 fluoxetine versus amineptine							
Brambilla 1995b	7	17.70 (2.60)	6	21.10 (6.30)		100.0	-0.68 [-1.81, 0.46]
Subtotal (95% CI)	7		6			100.0	-0.68 [-1.81, 0.46]
Test for heterogeneity: not applicable							
Test for overall effect: z=1.17 p=0.2							



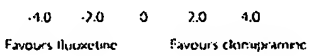
Analysis 02.02. Comparison 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 02 End of treatment mean absolute weight (high is better)

Review: Antidepressants for anorexia nervosa

Comparison: 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 02 End of treatment mean absolute weight (high is better)

Study	clomipramine N	clomipramine Mean(SD)	fluoxetine N	fluoxetine Mean(SD)	Standardised Mean Difference (Random) 95% CI	Standardised Mean Difference (Random) 95% CI
01 fluoxetine versus clomipramine						
Ruggiero 2001	13	38.69 (9.38)	10	42.70 (7.54)		-0.45 [-1.28, 0.39]



Analysis 02.03. Comparison 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 03 Mean percentage of weight increase (high is better)

Review: Antidepressants for anorexia nervosa

Comparison: 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 03 Mean percentage of weight increase (high is better)

Study	clomipramine N	clomipramine Mean(SD)	fluoxetine N	fluoxetine Mean(SD)	Standardised Mean Difference (Random) 95% CI	Standardised Mean Difference (Random) 95% CI
01 fluoxetine versus clomipramine						
Ruggiero 2001	13	3.26 (6.48)	10	4.52 (5.89)		-0.19 [-1.02, 0.63]

-4.0 -2.0 0 2.0 4.0

Favours fluoxetine Favours clomipramine

Analysis 02.04. Comparison 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 04 End-point mean scores in Eating Disorders Inventory (EDI)

Review: Antidepressants for anorexia nervosa

Comparison: 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 04 End-point mean scores in Eating Disorders Inventory (EDI)

Study	fluoxetine N	fluoxetine Mean(SD)	other AD N	other AD Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 fluoxetine versus nortriptyline							
Brambilla 1995a	15	41.40 (27.90)	7	39.00 (20.50)		100.0	0.09 [-0.81, 0.99]
Subtotal (95% CI)	15		7			100.0	0.09 [-0.81, 0.99]
Test for heterogeneity: not applicable							
Test for overall effect: z=0.19 p=0.8							
02 fluoxetine versus amineptine							
Brambilla 1995b	6	74.00 (13.70)	7	46.20 (16.40)		100.0	1.70 [0.36, 3.04]
Subtotal (95% CI)	6		7			100.0	1.70 [0.36, 3.04]
Test for heterogeneity: not applicable							
Test for overall effect: z=2.48 p=0.01							

-4.0 -2.0 0 2.0 4.0

Favours fluoxetine Favours other AD

Analysis 02.05. Comparison 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 05 End-point mean scores in Hamilton Depression Scale (HRS-D)

Review: Antidepressants for anorexia nervosa

Comparison: 02 ANTIDEPRESSANT VS ANTIDEPRESSANT

Outcome: 05 End-point mean scores in Hamilton Depression Scale (HRS-D)

Study	fluoxetine N	fluoxetine Mean(SD)	other AD N	other AD Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 fluoxetine versus nortriptyline							
Brambilla 1995a	15	11.00 (6.30)	7	6.00 (3.40)		100.0	0.86 [-0.08, 1.80]
Subtotal (95% CI)	15		7			100.0	0.86 [-0.08, 1.80]
Test for heterogeneity: not applicable							
Test for overall effect z=1.79 p=0.07							
02 fluoxetine versus amineptine							
Brambilla 1995b	6	11.20 (6.90)	7	11.20 (7.80)		100.0	0.00 [-1.09, 1.09]
Subtotal (95% CI)	6		7			100.0	0.00 [-1.09, 1.09]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							

-4.0 -2.0 0 2.0 4.0

Favours fluoxetine Favours other AD

Analysis 02.06. Comparison 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT, Outcome 06 End-point mean scores in Hamilton Anxiety Scale (HRS-A)

Review: Antidepressants for anorexia nervosa

Comparison: 02 ANTIDEPRESSANT VS. ANTIDEPRESSANT

Outcome: 06 End-point mean scores in Hamilton Anxiety Scale (HRS-A)

Study	fluoxetine N	fluoxetine Mean(SD)	other AD N	other AD Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 fluoxetine versus nortriptyline							
Brambilla 1995a	15	54.30 (29.60)	7	18.90 (17.90)		100.0	1.28 [0.29, 2.27]
Subtotal (95% CI)	15		7			100.0	1.28 [0.29, 2.27]
Test for heterogeneity: not applicable							
Test for overall effect z=2.53 p=0.01							
02 fluoxetine versus amineptine							
Brambilla 1995b	6	50.40 (34.80)	7	37.00 (31.00)		100.0	0.38 [-0.72, 1.48]
Subtotal (95% CI)	6		7			100.0	0.38 [-0.72, 1.48]
Test for heterogeneity: not applicable							
Test for overall effect z=0.67 p=0.5							

-4.0 -2.0 0 2.0 4.0

Favours fluoxetine Favours other AD

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CURRENT CONCEPTS IN CLINICAL NUTRITION

Nutrition, Immunology, Neuroscience and Behavior

GUEST EDITOR:

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Anorexia During Acute and Chronic Disease

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Date accepted: 11 January 1996

ABSTRACT

Anorexia is associated with disorders of all systems. Anorexia represents a consistent clinical manifestation during acute and chronic pathophysiological processes (infection, inflammation, injury, toxins, immunological reactions, malignancy and necrosis). Anorexia during disease can be beneficial or deleterious depending on the timing and duration. Temporary anorexia during acute disease may be beneficial to an organism since a restriction in the intake of micro- and macronutrients will inhibit bacterial growth. Long-term anorexia during chronic disease, however, is deleterious to an organism and may be associated with cachexia, which can ultimately result in death. Various mechanisms participate in the anorexia observed during disease, including cytokine action. Anorexia induced by cytokines is proposed to involve modulation of hypothalamic-feeding associated sites, prostaglandin-dependent mechanisms, modifications of neurotransmitter systems, gastrointestinal, metabolic, and endocrine factors. In addition, the anorexia-cachexia syndrome is multifactorial and may involve chronic pain, depression or anxiety, hypogeusia and hyposmia, chronic nausea, early satiety, malfunction of the gastrointestinal system, metabolic alterations, cytokine action, production of other anorexigenic substances and/or iatrogenic causes (chemotherapy, radiotherapy). Cachexia may result not only from anorexia and a decreased caloric intake, but also from malabsorption and losses from the body (ulcers, hemorrhage, effusions), or a change in body metabolism. Research has focused on potential interventions to modify anorexia during disease and the anorexia-cachexia syndrome. Nutritional modifications and the use of specific steroids (such as megestrol acetate) are being tested in the clinical setting. Understanding the specific mechanisms responsible for anorexia during disease as well as their interactions is essential to develop interventions for the control of anorexia (during a critical time in a specific disease), and to devise less toxic immunotherapeutic regimens using cytokines. *Nutrition* 1996;12:69–78

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INTRODUCTION

Acute (inflammatory, infectious) and chronic (neoplastic, necrotic, infectious) pathophysiological processes in the human and other species are frequently accompanied by anorexia. Anorexia is also one of the most common neurological manifestations observed during chemotherapy, radiotherapy and/or immunotherapy (for viral diseases, cancer or autoimmune processes) in humans. Anorexia also occurs as an adverse effect of numerous pharmacological treatments (e.g., antihypertensive, digitalics, diuretics), and during opiate withdrawal syndrome.

This article presents an integrative view of anorexia (loss of appetite) that occurs as a clinical manifestation during acute and chronic disease. Anorexia nervosa as a specific syndrome within eating disorders will not be discussed. Anorexia as a clinical manifestation should also be discriminated from: i) decreased eating (or stopping eating prematurely) because of mechanical problems in gastric filling or emptying; ii) sitophobia (fear of eating because of potential abdominal pain or other unpleasant sensations; psychoneurotic abhorrence of food) that may be associated with, for example, regional enteritis or chronic mesenteric vascular insufficiency; and odynophagia (pain upon swallowing), which can be associated with anxiety about eating; iii) food intolerances; and iv) early satiety (normal appetite followed by feeling of fullness after eating a small quantity of food). It is important to note, however, that early satiety is present in a significant number of patients with cancer exhibiting anorexia.

ANOREXIA DURING DISEASE

Anorexia is associated with disorders of all systems. It represents a consistent clinical manifestation during infections and cancer, and chronic pain from any source. Anorexia is associated with endocrine (for example, Addison's disease, hyperparathyroidism, panhypopituitarism, pheochromocytoma), gastrointestinal (gastric carcinoma, infectious processes, inflammatory bowel disease), hepatic (acute hepatitis), pancreatic, biliary (cholecystitis), renal (chronic renal failure and resulting uremia), pulmonary (chronic obstructive lung disease), cardiovascular (congestive heart failure), immune, hematological, and neurological (hypothalamic) disorders as well as psychiatric illnesses (depression), nutritional deficits (iron, thiamin, folate and cyanocobalamin deficiencies) and others (e.g., connective tissue diseases including rheumatoid arthritis and systemic lupus erythematosus). Thus, anorexia is a nonspecific but prominent clinical manifestation in an extensive variety of clinical disorders.

Short-Term Anorexia During Disease

Anorexia during organic disease can be beneficial or deleterious to an organism depending on the timing and duration. It seems inconsistent that anorexia occurs when the organism requires energy to generate the acute phase response including fever. However, force feeding during infection can increase morbidity and mortality.[1,2] Therefore, it is possible that the restriction in the intake of micro- and macronutrients may be a role of the temporary anorexia during infection. For example, a decrease in the intake of iron concurrently to its sequestration in the liver and spleen during the acute phase response results in the decrease of circulating iron levels. Since iron is essential to the growth and survival of pathogenic organisms, a decrease in blood iron levels in the presence of fever will inhibit bacterial growth because bacteria proliferate by chelating free iron in the circulation.[3]

It is proposed that cytokines participate in the anorexia during disease (see below). Evidence shows that cytokine administration differentially affects macronutrient intake. Interleukin-1β-treated animals, for example, ingest relatively the same or more quantity of carbohydrate and significantly less protein,[4,5] whereas relative fat intake remains unchanged[4] or decreases.[5] This suggests that maintenance or enhancement of carbohydrate intake (with its rapid energy yielding) may be a response to the increased demands of the host produced by the acute phase response.

Long-Term Anorexia During Disease

Diseases with long-term anorexia may be associated with cachexia. Cachexia is characterized by a progressive wasting of adipose and muscle tissues accompanied by anorexia, malnutrition and body weight loss, asthenia, and anemia. Cachexia is observed in chronic pathological processes including cancer,[6] human immunodeficiency virus (HIV) infection,[7] chronic bacterial and parasitic diseases, chronic inflammatory bowel disease,[8] chronic liver disease,[9] chronic obstructive pulmonary disease,[10] chronic cardiovascular disease,[11] and rheumatoid arthritis.[12] Cachexia devitalizes an organism, making it susceptible to secondary pathologies, and if uncontrolled, cachexia can ultimately result in death. The specific mechanisms of cachexia (neurological, metabolical, endocrinological) and their interactions are under intensive investigation.

ANOREXIA DURING IMMUNOTHERAPY

Anorexia is also induced by the exogenous administration of various cytokines in mammals, including immunotherapy in humans.[13,14] Evidence suggests that action of cytokines (immunomodulators such as interleukin-1, tumor necrosis factor-α, interferon) and other immunomodulatory molecules[15] on peripheral and/or central nervous system target sites are part of the regulatory signals that induce anorexia. Cytokine-induced anorexia can be blocked with the appropriate receptor antagonists,[16,17] monoclonal antibodies,[18] and other inhibitors.[19] This evidence suggests a role for cytokines in anorexia during pathophysiological processes. In addition to immunotherapy, radiotherapy and chemotherapy can also be associated with anorexia, emesis, and chronic nausea.

RELATIONSHIP BETWEEN ANOREXIA AND OTHER COMMON NEUROLOGICAL MANIFESTATIONS

Other neurological manifestations frequently occurring during acute disease include fever and sleep changes. These manifestations, however, can be dissociated from anorexia. Cytokines administered into the brain (in the picogram-nanogram range) or peripherally (in the microgram range or during immunotherapy) induce anorexia,[16,18,20] fever,[21] sleep changes,[22] and neuroendocrine alterations[23] that resemble those observed during disease. These effects depend on the cytokine used, its concentration, and duration and timing of administration. Cytokine-induced and microbialproduct-induced anorexia can be dissociated from their fever-inducing effect.[4,16,18,24-26] For example, sodium salicylate and other antipyretics block fever induced by bacterial endotoxin (a lipopolysaccharide) but do not restore appetite. This is consistent with the clinical observation that patients receiving antipyretic therapy exhibit anorexia. Evidence also shows that the threshold of cytokine concentrations required to induce anorexia is lower relative to the threshold needed to induce fever.

Anorexia, pyrogenesis, and somnogenesis during acute disease are interactive (and probably essential) contributors to the host recovery from disease. Fever can suppress the growth of microorganisms and enhance immunological responses by heightening mononuclear cell and lymphocyte activities and antibody synthesis.[27] Increased sleep is evident during infectious diseases. Sleepiness during disease decreases the activity of an individual, resulting in the conservation of energy. Better prognosis and a reduction of pathophysiological indicators of infectious processes are correlated with enhanced sleep.[28]

The activation of the immune system during disease is accompanied by activation of the neuroendocrine system.[29] Feedback loops in the hypothalamic-pituitary-adrenal gland axis involve cytokines. Various cytokines induce the synthesis and release of corticotropin-releasing factor from the hypothalamus, ACTH from

the pituitary, and glucocorticoids from the adrenal glands. The increased levels of circulating glucocorticoids in turn inhibit several immune system functions (and inflammatory responses) including the synthesis and release of interleukin-1 and tumor necrosis factor-α.[25] This physiological immunosuppression may prevent overresponsiveness of the immune system.

MECHANISMS RESPONSIBLE FOR ANOREXIA

Feeding behavior involves a variety of psychological factors, neuronal and humoral mechanisms, and gastrointestinal, metabolic, and nutrient factors.[30] During pathophysiological processes, modifications in one or more various components participating in the regulation of feeding will result in anorexia. Although peripheral and central mechanisms may be involved in anorexia during disease, the loss of appetite will eventually result from modifications in the final common pathway for appetite control that depends on central nervous system mechanisms.

How anorexia is induced in a specific disease or which factors are predominantly responsible for anorexia in a disease is incompletely understood. However, various factors and mechanisms have been proposed to participate in the anorexia observed during disease including cytokine action. For example, anorexia induced by interleukin-1α or -1β has reported to involve the following: cytokine action in peripheral and central nervous system target sites; modulation of hypothalamic-feeding associated sites;[31,32] prostaglandin-dependent mechanisms;[33-36] modifications of neurotransmitter systems (catecholamines, serotonin);[37,38] gastrointestinal (inhibition of gastric motility,[24,39] gastric emptying[40] and gastric acid secretion,[41] and modulation of intestinal motility[42]) and endocrine (corticotropin-releasing factor,[43] cholecystokinin,[44] glucagon and insulin[45]) factors.

Characterization of interactions between cytokines and peptides is also essential to understand cytokine- and disease-induced anorexia. For example, evidence shows that hypothalamic concentration and release of neuropeptide Y (a potent orexigenic or feeding-stimulating factor) is reduced in anorectic tumor-bearing rats.[46] Neuropeptide Y is also a less potent stimulator of feeding in tumor-bearing rats relative to the control animals; this deficit in neuropeptide Y action may result from a hypothalamic decrease of neuropeptide Y receptor affinity (which decreases progressively as the rats become more anorectic).[47] On the other hand, a correlation between food intake and cerebrospinal fluid interleukin-1 concentrations in anorectic tumor-bearing rats has been reported.[48] These studies suggest the presence of a central nervous system dysregulation of neuropeptide Y feeding-related mechanisms associated with an enhanced interleukin-1 activity in tumor-bearing rats. This is also supported by evidence showing that intracerebroventricularly administered neuropeptide Y blocks and reverses the anorexia induced by the intracerebroventricular administration of interleukin-1β at estimated pathophysiological and pharmacological (cerebrospinal fluid) concentrations in rats.[146] Blockage and reversal of interleukin-1β-induced anorexia by neuropeptide Y suggest the importance of studying endogenous cytokine-peptide interactions in the regulation of feeding. Understanding these interactions may produce strategies with potential therapeutic implications for chronic diseases associated with long-term anorexia.

Anorexia Induced by Cytokines and Microbial Products

Infections, injury (burns, trauma), toxins, acute and chronic inflammatory processes, immunological reactions, malignancy, and necrosis stimulate the synthesis and release of cytokines in various cell systems.[45,49] Cytokines participate in the acute phase response characterized by local and systemic reactions including anorexia. Pathophysiological processes and immunotherapy with cytokines are associated with anorexia. Therefore, anorexigenic cytokines (interleukin-1,[16,20] interleukin-6,[50] tumor necrosis factor-α,[20,32] interferon,[25] interleukin-8,[18] and other chemokines/intercrines,[51] and platelet activating factor[50]) could participate in the anorexia observed during pathophysiological processes and immunotherapy.

Peripheral administration (intravenous, intraperitoneal, or subcutaneous) of cytokines induces anorexia in humans and animals. Administration of microbial products that induce anorexigenic cytokine release also results in anorexia. These microbial products (bacterial endotoxin or a lipopolysaccharide from gram-negative, and muramyl dipeptide from gram-positive bacteria) are potent anorexigenic agents,[52,53] an effect that could be direct and/or mediated by anorexigenic cytokines (interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor-α). The anorexigenic effect of endotoxin and muramyl dipeptide could participate in the anorexia observed during gram-negative and gram-positive infections, respectively. Dr. Wolfgang Langhans (Swiss Federal Institute of Technology, Switzerland) will focus his contribution to this series on this issue, that is, the clinical implications of the modulation of ingestive behavior in response to bacterial products.

In animal models, administration of cytokines into the third cerebral ventricle (i.e., close to the critical hypothalamic regions that participate in the regulation of feeding and drinking) induces anorexia at estimated pathophysiological concentrations (picogram–low nanogram range: femtomolar–picomolar range) reported in the cerebrospinal fluid or brain.[16,18,25,50] Because the peripheral administration of cytokines consistently requires doses in the microgram range to induce anorexia, the data suggest that low doses of cytokines administered into the brain induce anorexia by direct action in the central nervous system. It is important to note, however, that insufficient evidence is available in humans to establish any conclusion regarding the relationship between cytokine concentrations in body fluids and anorexia. In addition, cytokines acting in an autocrine and/or paracrine manner during disease may induce neurological manifestations without exhibiting increased concentrations in the circulation. The availability of commercial systems will provide information on the autocrine-paracrine-endocrine mechanisms involved in cytokine action, as well as the determination of cytokines as markers of diagnosis, prognosis, and/or therapeutic efficacy during different diseases.

The administration of a particular cytokine may induce the secondary release of other cytokines. Based on the evidence, a multi-cytokine interaction inducing anorexia during disease is proposed. This is supported by the following: (1) The interaction among cytokines that occurs during activation of the immunoregulatory network. (2) The synergistic cytokine interactions inducing anorexia.[20,54] These studies have shown that interleukin-1α or β and tumor necrosis factor-α have a synergistic effect in inducing anorexia. (3) The evidence demonstrating that only a subset of cytokines released during activation of the immune system induces anorexia.[51] (4) The data indicating that various categories of cytokines have different potencies inducing anorexia [interleukin-1, for example, is significantly more potent ($p < 0.01$) in suppressing feeding relative to other cytokines].[16,51] (5) The different alterations in the microstructure of feeding (assessed by computerized behavioral-monitoring systems) induced by various cytokines in rodents at estimated pathophysiological concentrations.[16,18,25,55] Interleukin-1β induces short- and long-term anorexia by reducing meal size and meal duration at estimated pathophysiological concentrations in the cerebrospinal fluid,[16] and at pharmacological concentrations by also decreasing meal frequency,[16] while interferon induces anorexia by reducing meal size and meal duration,[25] and interleukin-8 by reducing meal size exclusively.[18] These precise changes in meal parameters suggest differential actions of interleukin-1β, interferon and interleukin-8 in central nervous system feeding-associated sites. In a subsequent paper of the series, Dr. Akira Uehara (Asahikawa Medical College, Japan) will elaborate on this issue, specifically on the interaction between cytokines

and the control of ingestive behavior including the clinical implications.

Action of Cytokines in the Brain and Anorexia

Intensive research focuses on the source of cytokines in the brain. Cytokines can affect the central nervous system to induce anorexia and other neurological manifestations via: (1) transport of cytokines from the peripheral circulation to the brain-cerebrospinal fluid across the circumventricular organs—which lack a blood-brain barrier—and possibly through the blood-brain barrier;[56] (2) release of cytokines from immune system cells that can cross the blood-brain barrier during neurological pathophysiological (e.g., inflammatory) processes;[57] (3) generation of chemical mediators (e.g., prostaglandins) and release of humoral factors (e.g., peptides) that can act on peripheral and/or central nervous system target sites; (4) afferent signaling through the peripheral and autonomic nervous systems,[58] as has been demonstrated for other peptides; and (5) local brain–spinal cord production of cytokines from intrinsic (brain) macrophages,[59] endothelial cells of the cerebrovasculature,[45] microglia,[60] astrocytes,[61] and possibly neuronal components,[62–64] in response to the appropriate stimulation. Locally produced cytokines in the brain have been demonstrated to regulate intrinsic feedback systems through paracrine, yuxtacrine and autocrine mechanisms[45] and to induce neurological manifestations ([16,18,25]).

A variety of important neuroanatomical substrates participate in the regulation of feeding, including hypothalamic areas/nuclei (e.g., arcuate, dorsomedial, lateral, paraventricular, ventromedial), brainstem nuclei/areas (e.g., area postrema, catecholaminergic brainstem neuronal groups, dorsal motor nucleus of the vagus, locus coeruleus, nucleus ambiguus, nucleus tractus solitarius, parabrachial nuclei, raphe nuclei), neuroanatomical sites associated with sensory and chemical senses, cortical areas, hippocampus, amygdala, nucleus accumbens, substantia nigra, caudate nucleus–putamen (striatum) and globus pallidus, ventral tegmental area, and integrative sympathetic and parasympathetic pathways. These neuroanatomical sites and pathways operate in an integrative manner to prepare the animal to focus on and select external stimuli (sensory systems and chemical senses), activate feeding related responses and sensory-motor feedback systems, and activate reward, satiety, aversion and other processes. One of the best-studied neuroanatomical feeding-associated brain sites is the hypothalamus. Hypothalamic neurotransmitter/neuropeptide/neuromodulatory feeding-associated mechanisms have been studied. For example, various cytokines act directly and specifically on hypothalamic feeding-associated sites to induce anorexia. Cytokine-induced anorexia involves the modulation of specific neurons that are proposed to participate in the control of feeding, i.e., glucose-sensitive neurons in the lateral hypothalamic area (LHA)[32] and hypothalamic ventromedial nucleus (VMN).[65] This model predicts that inhibition of LHA and activation of VMN will result in anorexia. Application of interleukin-1β or tumor necrosis factor-α specifically and reversibly suppresses the neuronal activity of the glucose-sensitive neurons in the LHA,[32] while interleukin-1β- or interferon-α excites the glucose-sensitive neurons in the VMN.[65] Interleukin-1β, tumor necrosis factor-α and interferon-α have little effect on the glucose-insensitive neurons in the LHA and VMN, indicating specificity of action.

At the molecular level, pathophysiological concentrations of interleukin-1β (observed in the cerebrospinal fluid of patients with human immunodeficiency virus infection and bacterial meningitis) inhibit the neuronal voltage-gated calcium channel currents.[66] This action of interleukin-1β is prevented by the concomitant application of interleukin-1 receptor antagonist (a competitive inhibitor), suggesting mediation through a direct interaction with an interleukin-1 membrane receptor site.[66] The modulation of the inward calcium channel current (and hence calcium permeability) by interleukin-1β may play a role in regulating neuronal excitability and neurotransmitter release-associated mechanisms. This is supported by the characteristics of the interleukin-1β-induced long-lasting LHA and VMN neuronal activity modulation that may be associated with the long-term anorexia induced by the cytokine. A decrease in calcium influx in LHA glucose-sensitive neurons may result in inhibition, while a decrease in calcium influx in VMN glucose-sensitive neurons may inhibit the defined calcium-dependent potassium conductance in these neurons, leading to maintenance of intracellular potassium, then depolarization and increase in neuronal activity.

Taste Aversion and Anorexia

It is proposed that taste aversions may contribute to the anorexia observed during gram-positive or gram-negative bacterial infection,[67] or during cytokine (interleukin-1β, tumor necrosis factor-α) administration.[58] However, the development of conditioned taste aversions in response to the cerebral ventricular administration of interleukin-1β in the rodent has been reported only with high doses of the cytokine.[68,69] In fact, the aversive effect of peripherally administered interleukin-1β is rather weak, and presumably not involved in the anorexic effect of interleukin-1.[70] Nevertheless, because endogenous cytokine interactions occur during disease, it remains to be determined whether the cytokine network induces anorexia through taste aversions in vivo. Clinical data suggest that patients with cancer can develop learned aversions to specific foods eaten during the growth phase of the tumor or as a reaction the nausea-inducing chemotherapy. Unpalatability and aversion to meat are predominant. In fact, it is recommended that patients under chemotherapy avoid protein-rich foods, which have a higher probability of inducing aversions relative to the carbohydrate-rich foods.

MECHANISMS OF CACHEXIA

Anorexia is pivotal to the condition of cachexia. Anorexia-cachexia syndrome in cancer patients may result from pain, depression or anxiety, hypogeusia and hyposmia (and other taste and olfaction abnormalities), chronic nausea, vomiting, early satiety, malfunction of the gastrointestinal system (due to direct tumor encroachment, delayed digestion, malabsorption, gastric stasis and associated delayed emptying, and/or atrophic changes of the mucosa), metabolic shifts, cytokine action, production of other anorexigenic substances by tumor cells, and/or iatrogenic causes such as chemotherapy and radiotherapy. The main consideration is that the anorexia-cachexia syndrome is multifactorial and involves metabolic and immune changes (mediated either by the pathological process, i.e., tumor, or by host-derived chemical factors), and does not depend on a single cause. In addition, cachexia may result not only from anorexia and a decreased caloric intake, but also from malabsorption and losses from the body (ulcers, hemorrhage, effusions) or a change in the body metabolism. In any case, the major deficit of a cachectic organism is a negative energy balance in which food intake is less than energy output, resulting in a net loss of body weight.

Cytokines and Cachexia

A brief description on this issue is presented. Dr. Patrick Matthys (Rega Institute, Belgium) will discuss the relationship between cytokines and the induction or progression of cachexia in a later article of the series.

Cytokine-induced anorexia is proposed to participate in the development of cachexia during various diseases. Interleukin-1,[71,72] interleukin-6[73–75] [and its subfamily members such as ciliary neurotrophic factor[76–78] and leukemia inhibitory factor,[73] which induce anorexia with different potencies and effectiveness[145]], interferon-γ,[79,80] tumor necrosis factor-α,[6,71,81] and brain-derived

neurotrophic factor[82] have been associated with various cachectic animal models.

The lines of evidence implicating cytokine involvement in cachexia include the following. (1) Tumor necrosis factor-α transgenic mice.[83] (2) Passive immunization against cytokines in cachectic tumor-bearing rodents.[74,79,84] Treatment of rodents bearing tumors with monoclonal antibodies against the interleukin-1 receptor or tumor necrosis factor-α inhibits tumor growth and improves feeding significantly.[72] These effects, however, have not been observed in all animal models of cancer cachexia.[79] (3) Inoculation of mice with cytokine-producing tumor cells.[80,85] Oliff et al.,[85] for example, compared the effects of the tumor necrosis factor-α-secreting tumor to those of the same tumor without the gene for tumor necrosis factor-α; in this study, mice bearing the tumor necrosis factor-α-secreting tumor developed progressive anorexia and body weight loss relative to the animals bearing the tumor without the gene for tumor necrosis factor-α.[85] (4) Transplants of malignant tumors into rodents.[48,86] (5) Data suggesting a link between cerebrospinal fluid interleukin-1 concentrations and the progression of anorexia in tumor-bearing rats.[48] Elevated levels of circulating tumor necrosis factor-α have also been reported in tumor-bearing rats, and levels correlate with parameters of cachexia and return to normal following resection of the tumor.[79] In any case, the development of cachexia may imply a chronic multi-cytokine interaction. It is important to note that, in animal studies, chronic administration of interleukin-1α or -1β is accompanied by the development of tolerance to the anorexic effect.[87-89] Tolerance is not observed when interleukin-1β is injected repeatedly (every 2nd day, i.e., when the anorexic effect of the preceding dose has subsided),[89] and in fact, repeated intraperitoneal injections of interleukin-1β result in sensitization to the anorectic effect of interleukin-1β.[55] It is possible that tolerance during the chronic infusion develops through receptor mechanisms such as the receptor-mediated endocytosis and associated down-regulation, activation of a decoy receptor, and receptor negative cooperativity to maintain cytokine sensitivity at low concentrations but attenuation of the response with higher concentrations. Generation of inhibitory signals with high concentrations, an increase in the degradative capacity of the cytokine administered, and involvement of endogenous glucocorticoids are also factors to be considered; antibodies to the interleukin-1 preparation used are not significantly detected,[89] suggesting that a humoral immune response may not be involved in the development of tolerance.

Human studies also support cytokine involvement in cachexia. Controversy has been focusing on the requirement of increased cytokine concentrations in the circulation or other body fluids (e.g., cerebrospinal fluid) to demonstrate cytokine involvement in cachexia. (For example, studies using the cachexia-inducing murine tumor MAC16 model system have not supported the involvement of tumor necrosis factor-α or interleukin-6 in cachexia;[90,91] and cancer patients in various studies have not exhibited increased circulating levels of cytokines.) Cytokines, however, not only act in an endocrine fashion, but also in paracrine (on neighbor cells), autocrine (on the same cell) and intracrine (inside the cell that produces it) manners, activities that cannot be detected in the circulation. In fact, paracrine interactions represent a predominant cytokine mode of action. This suggests that cytokines may be involved in cachectic processes not associated with increased cytokine concentrations in the circulation. This explanation may account for the inconsistent finding of circulating cytokines in cachectic patients. Various studies, however, have associated pathological processes with increased levels of cytokines (serum and/or cerebrospinal fluid) in a number of patients with: (i) various types of cancer;[6,92,93] (ii) the HIV syndrome;[7,94-96] (iii) chronic inflammatory bowel disease;[8] (iv) chronic liver disease;[9] (v) chronic obstructive pulmonary disease;[10] (vi) cardiac cachexia (during congestive heart failure);[11] and (vii) the flaring phase of rheumatoid cachexia[12] and juvenile rheumatoid arthritis.[97]

Cytokines and Metabolic Alterations in Cachexia

Dr. MJ Tisdale (Aston University, UK) will elaborate on the metabolic alterations associated with cachexia in a subsequent article of the series.

Here, a brief description is presented to comply with the objective of integration of the topic on anorexia during acute and chronic disease. Acute disease and the anorexia-cachexia syndrome are associated with a myriad of metabolic alterations including hypertriglyceridemia and lipolysis, which may be prominent. Cytokines (interleukin-1β, interleukin-6, tumor necrosis factor-α, interferon) increase the rate of lipolysis[98,99] and modify lipoprotein lipase activity.[100] Cytokine-induced hypertriglyceridemia occurs in vivo.[99,101] It has been suggested that hypertriglyceridemia and other changes in lipid metabolism during infectious disease may be beneficial to the host, as lipoproteins can decrease the toxicity of bacteria and viruses by binding, for example, lipopolysaccharide.[99,101] During anorectic/cachectic conditions, the organism maintains triglyceride-rich lipoproteins to sustain the protective effects of lipoproteins.[101] Lipid mobilization also may be required to sustain the elevated relative energy expenditure observed in cancer patients.[102]

Cachexia is also accompanied by other metabolic alterations. Protein turnover is accelerated with elevated hepatic protein synthesis and increased skeletal muscle breakdown. These changes in protein and lipid metabolism result in the loss of body protein and fat mass with the gain in total body water.[103] Cytokines (e.g., tumor necrosis factor-α) also induce alterations in protein metabolism. In an ensuing article of the series, Dr. Pierre Demacker and Dr. Jos WM van der Meer (St. Radboud University Hospital, The Netherlands) will discuss on the clinical implications of the effects of cytokines on carbohydrate, lipid and protein metabolism.

In general, increased resting energy expenditure in body-weight-losing cancer patients has been consistently reported[102] despite the reduced dietary intake, indicating a systemic dysregulation of host metabolism. This is in contrast to the lower metabolic rates and adaptation that normal subjects exhibit after starvation. During cachexia, the organism is maintained in a constant negative energy balance. This can rarely be explained by the actual energy and substrate demands by tumors in patients with cancer. Chemical factors derived from tumor or host cells (peptides, cytokines) have been proposed to participate in the anorexia and other manifestations observed during cachectic processes. Neurotransmitters (e.g., serotonin) and their precursors (e.g., tryptophan) may also play important roles in cancer anorexia.[104] Parabiotic models have shown that anorexia in a tumor-bearing animal can be transmitted via the circulation to a non-tumor-bearing partner with the resulting body weight loss in both partners. Tumor-derived products including lipid-mobilizing factors have been implicated in the development of cachexia in animal models and in humans.[105] Tumor-derived factors with anorexigenic activity include bombesin (produced by small cell lung cancer) and serotonin (produced by bronchial and gastrointestinal carcinoid tumors).

Based on the metabolic changes occurring in cachexia, it is possible that anorexia may be the result of the catabolic process, cytokine release and chemicals released by the tumor. Therefore, anorexia may be involved as partly the cause and partly the consequence of metabolic changes that occur in cachexia.

MODIFICATION OF ANOREXIA DURING ACUTE AND CHRONIC DISEASE

Anorexia during acute disease (e.g., infections) could be beneficial to an organism. Anorexia during chronic disease, however, could be deleterious to an organism. It is recognized that malnourished patients have lower prognosis and a higher incidence of

complications. Research has been focusing on developing potential interventions to modify anorexia during chronic disease and the anorexia-cachexia syndrome. Two of these approaches are under intensive clinical investigation: nutritional modifications and the use of specific steroids.

Modification of Anorexia Through Nutritional Substrates

Dietary factors, and enteral and parenteral nutrition modify the production and activity of cytokines.[105] In healthy human volunteers, dietary fish oil [rich in the long-chain ω-3 (or n-3) polyunsaturated fatty acids] supplementation inhibits the in vitro production of interleukin-1,[107,108] interleukin-6,[107] and tumor necrosis factor-α.[108] Supplementation with ω-3 fatty acids also significantly reduces in vitro production of interleukin-1β, interleukin-6 and tumor necrosis factor-α in both healthy young and older women, with a greater reduction in older women;[109] the reduction in interleukin-2 production is significant only in the older population, which also exhibits a decreased T-cell mitogenesis.[109] Clinical studies have also reported that dietary supplementation with ω-3 fatty acids decreases in vitro production of interleukin-1 from monocytes of rheumatoid arthritis patients.[110]

The inhibition of cytokine production by ω-3 fatty acids is a long-lasting phenomenon. In the study of Endres et al.,[108] the release of interleukin-1α and -1β, and tumor necrosis factor-α was further inhibited 10 wk after the end of the ω-3 fatty acid supplementation; production of cytokines returned to the presupplementary ω-3 fatty acid level 20 wk after the end of the supplementation.[108]

Long-chain ω-3 (or n-3) polyunsaturated fatty acids include eicosapentaenoic (C20:5ω-3) and docosahexaenoic (C22:6ω-3) acids that derive from α-linolenic acid (C18:3ω-3) and undergo biological transformation to trienoic eicosanoids. These eicosanoids alter the production of inflammatory mediators (including cytokine production). Suppression of cytokine production occurs by inhibiting the cyclooxygenase pathway, hence prostaglandin[111] and leukotriene[111,112] synthesis. Eicosapentaenoic acid is a potent suppressor of cytokine (interleukin-1, -2, -6 and tumor necrosis factor-α) secretion in vitro and also inhibits T-cell proliferation.[113] Eicosapentaenoic acid competes for the incorporation of arachidonic acid in membrane phospholipids and inhibits the conversion to prostanoids. Eicosapentaenoic acid can be converted to 3-series prostanoids or 5-series leukotrienes which differ in potency relative to the analogous 2nd and 4th series. For instance, leukotriene B_5, by competition with leukotriene B_4, reduces the inflammatory response, and prostaglandin E_3 and leukotriene B_5 are more effective than prostaglandin E_2 and leukotriene B_4 in reducing lymphocyte proliferation.[114] The evidence also suggests that the action of eicosanoids on cytokine production may differ depending on the type (and concentration) of eicosanoid involved. Thromboxane B_2, for example, depending on its dose, may have both inhibitory or stimulatory effects on the synthesis of interleukin-2.[113]

Feeding of fish oil also diminishes the biological activities of cytokines, including the anorexigenic effect induced by interleukin-1[33] and tumor necrosis factor-α[115] in animal models. Dietary ω-3 fatty acid supplementation also inhibits pyrogenic and thermogenic responses to interleukin-1β in rodents.[116] A fish oil-enriched diet significantly inhibits the tumor-induced weight loss in animal models with tumor-induced cachexia.[117] Eicosapentaenoic acid inhibits lipolysis in adipocyte cultures from cachectic animals,[118] suggesting an action in preserving body weight. [Based on the previous description, the model predicts that inhibition of the cyclooxygenase pathway, hence prostaglandin synthesis, will be associated with a decrease of various biological activities induced by interleukin-1β. In fact, previous studies have shown that ibuprofen, indomethacin, and other inhibitors of prostaglandin synthesis attenuate the ano-rexia induced by the peripheral administration of interleukin-1β.[33-36] Both cyclooxygenase and lipoxygenase inhibitors are effective.[34] It remains to be determined whether these findings are replicable under various conditions associated with short- and long-term anorexia.]

Studies show, however, that different classes of lipids differentially modify the synthesis and biological actions of cytokines (resulting in immunosuppression and antinflammation, or in immunoenhancement) depending on the lipid subclass, amount, durations of supplementation, combination with other nutrients such as total parenteral nutrition, immune cell activation, in vitro versus in vivo systems, and biological idiosyncrasy (age, weight, sex, diet and activity).[106,119] For example, dietary supplementation with ω-3 fatty acids significantly reduced the content of interleukin-1β in lysates of PBMC, but did not affect PBMC or monocyte secretion of interleukin-1β, tumor necrosis factor-α, prostaglandin E_2 and leukotriene B_4 in healthy human subjects or in patients with insulin-dependent diabetic mellitus.[120]

The distinct actions of different lipids on immune system activities are under continuous investigation addressing the potential modes of action [e.g., modulation of eicosanoid production, changes in cell membrane structure (with its consequences on the membrane fluidity, receptor number and functioning, and membrane bound enzyme activities), and altered production and action of cytokines].

Therefore, nutritional modifications have the potential to influence anorexia and cachexia during chronic disease. Most feeding trials in human, however, have been of short duration (e.g., up to 12 wk), but because no major adverse effects have been reported and since the modifications at the cellular and physiological levels seem to be sustained, the potential applicability in anorexia and other neurological manifestations has to be approached with studies at the molecular, cellular, supracellular and clinical levels.

Dietary supplementation with ω-3 fatty acids affects various physiological and pathophysiological events, and thus its applicability to chronic disease states should include consideration of the extensive implications. For instance, ω-3 fatty acids are also essential for brain function in humans and other species. Membrane brain cells and organelles are extremely rich in ω-3 fatty acids. Because membrane levels of ω-3 fatty acids can influence behavioral, cognitive, and other functions, the state of well-being of a cachectic individual may also be improved through ω-fatty acid supplementation. Future well-controlled animal and clinical studies are required to assess the benefits (or potential disadvantages in older populations because of its suppressive effect on cell-mediated immunity) of dietary supplementation with ω-3 fatty acids in specific chronic disease conditions.

It is important to note that the emphasis of this discussion has been on the modification of anorexia through certain fatty acids. Aggressive parenteral or enteral nutrition has been attempted in patients with cancer cachexia and malnutrition. However, no conclusive effects have been shown on the overall patient survival, tumor response, adverse effects induced by antineoplastic therapy, and tumor growth.

Modification of Anorexia Through Specific Steroids

Specific chemical steroid derivatives such as megestrol acetate[121-124] are being investigated in the clinical setting to improve appetite in the cachectic patient. Megestrol acetate (17α-acetyloxy-6-methyl-4,6-pregnandiene-3,20-dione) is a synthetic, well-tolerated, orally active progestogen which has been found, in several clinical trials (including appropriate placebo-controlled, double-blinded trials) to enhance appetite, increase food intake, cause body weight gain, and improve the sense of well-being in a number of cachectic patients with cancer[123,125] and HIV infection.[121,122,124] The doses of megestrol acetate administered have been from 160 to 1,600 mg/24 h with a dose-response effect and an apparent plateau between 800 and 1,280 mg/24 h; although 800 mg/24 h appeared to be more effective than lower doses,

Loprinzi et al. found considerable appetite stimulation at the lower dose (160 mg/24 h) relative to the placebo.[123] In fact, Komblith et al.[126] reported a significant relationship between severity of side effects and increasing doses of megestrol acetate with better physical functioning, less psychological stress and overall improvement at 3 mo with 160 and 800 mg/24 hr relative to the 1600 mg/24 hr dose.[126] The effectiveness of low doses of megestrol acetate is an important factor considering the cost of long-term treatments with the steroid.

Because megestrol acetate is a progesterone derivative (with glucocorticoid activity), its potential effects on the endocrine system during long-term administration remain to be clarified. Recent clinical data show that prolonged administration of megestrol acetate can induce secondary adrenal suppression and adrenal insufficiency,[127] or Cushing's syndrome.[128] The long-term pharmacokinetics and drug interactions, as well as the action mechanism(s) of megestrol acetate on anorexia/cachexia, also require characterization. Present evidence suggests that megestrol acetate-induced stimulation of appetite may involve neuropeptide Y (a potent feeding-stimulating substance)[129] and modulation of calcium channels in the ventromedial hypothalamus,[130] while the body weight gain is attributable to a gain in fat mass.[121] Megestrol acetate may also inhibit cytokine production and counteract cytokine-induced anorexia.

Lipopolysaccharide- or interleukin-1-induced anorexia and other actions are attenuated by the pretreatment with corticosteroids (e.g., methylprednisolone, dexamethasone)[19,43] and other steroids. The effect of corticosteroids, however, seems to be short term. In cancer patients, short-term treatment with dexamethasone, methylprednisolone or prednisolone is associated with significant appetite enhancement, food intake increase and improvement in the feeling of well-being. Based on these clinical trials, corticosteroids are being proposed as palliative therapy in terminal cancer patients.[131,132] Corticosteroids are also useful as appetite enhancers in patients with asthenia. However, because of the broad metabolic effects, antiinflammatory and immunosuppressive, and neurological actions of these compounds, their potential therapeutic application for anorexia during disease is limited.

CONCLUSIONS

Anorexia is a consistent clinical manifestation during acute and chronic disease. Depending on the timing and duration, anorexia can be beneficial or deleterious to an organism. Long-term anorexia is associated with cachexia (anorexia-cachexia syndrome), a multifactorial process. Research focuses on potential interventions to modify anorexia during disease and the anorexia-cachexia syndrome. At present, clinical approaches have been directed toward improving the quality of life of patients with anorexia-cachexia syndrome. Because there is no effective treatment for this syndrome, clinical approaches vary considerably. When possible, the treatment of an underlying tumor appears to be the best general approach to reversing the state of cancer-associated anorexia. Nutritional modifications and the use of specific steroids (such as megestrol acetate) are being tested in the clinical setting. Pharmacological approaches also differ widely depending on clinical experience, effectiveness with long-term treatment, route of administration, side effects and cost. For example, metoclopramide (a benzamide dopaminergic antagonist with important antiemetic uses) is recommended by some investigators as a first-line approach to improve anorexia in patients with anorexia-cachexia syndrome, in particular for patients with cancer associated with delayed gastric emptying and gastroparesis.[133] The long-term effectiveness and toxicity of other compounds with appetite- and weight-enhancing effects such as cyproheptadine (with antihistaminic and antiserotonergic properties), hydrazine sulfate, dronabinol, nandrolone propionate, cannabinoids and hormones (e.g., growth hormone, somatostatin and insulin) is also being investigated for their potential applicability in patients with anorexia/cachexia.[134,135] Other compounds that inhibit cytokine production, such as pentoxifylline and thalidomide, have also been proposed to have application in cachectic disorders. Pentoxifylline has various immunomodulatory activities[136] and inhibits tumor necrosis factor-α production in patients with advanced cancer[137] and human immunodeficiency virus infection.[138] Based on these actions, the use of pentoxifylline in cachectic disorders[136,139] has been proposed; however, the clinical usefulness of pentoxifylline therapy remains to be determined since an uncontrolled pilot study in five patients with human immunodeficiency virus infection-associated cachexia did not show that pentoxifylline clearly benefited these patients.[140] Thalidomide has also been shown to inhibit tumor necrosis factor-α synthesis[141] and to suppress the activation of latent (and replication of) human immunodeficiency virus type 1;[141] however, the application of thalidomide to improve the patient's well-being and reduce the cachexia of the immunocompromised host remains to be determined.

In conclusion, understanding the mechanisms of anorexia during disease is critical in developing interventions aimed at the control of anorexia and other neurological manifestations (during a critical time in a specific disease), and in devising less toxic immunotherapeutic regimens using cytokines.

REFERENCES

1. Hart BL. Behavioral adaptations to pathogens and parasites: Five strategies. Neurosci Biobehav Rev 1990;14:273
2. Murray MJ, Murray AB. Anorexia of infection as a mechanism of host defense. Am J Clin Nutr 1979;32:593
3. Kontoghiorghes GJ, Weinberg ED. Iron: mammalian defense systems, mechanisms of disease, and chelation therapy approaches. Blood Rev 1995;9:33
4. Aubert A, Goodall G, Dantzer R. Compared effects of cold ambient temperature and cytokines on macronutrient intake in rats. Physiol Behav 1995;5:869
5. MacDonald H, Stamford S, McCarthy HD. Acute effect of peripheral interleukin-1β administration on macronutrient selection in the rat. Proc Nutr Soc 1993;52:358A
6. Tisdale MJ. Cancer cachexia. Anti-Cancer Drugs 1993;4:115
7. Coodley GO, Loveless MO, Merrill TM. The HIV wasting syndrome: A review. J Acquired Immune Defic Syndr 1994;7:681
8. Levine DS. Immune modulating therapies for idiopathic inflammatory bowel diseases. Adv Pharmacol 1994;25:171
9. Tilg H. The role of cytokines in the pathophysiology of chronic liver diseases. Int J Clin Lab Res 1993;23:179
10. Difrancia M, Barbier D, Mege JL, et al. Tumor necrosis factor-α levels and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;150:1453
11. Freeman LM, Roubenoff R. The nutrition implications of cardiac cachexia. Nutr Rev 1994;52:340
12. Roubenoff R, Rall LC. Humoral mediation of changing body composition during aging and chronic inflammation. Nutr Rev 1993;51:1
13. Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208
14. Meyers CA, Scheibel RR, Forman AD. Persistent neurotoxicity of systemically administered interferon-alpha. Neurology 1991;41:672
15. Plata-Salamán CR, Sonti G, Borkoski JP. Modulation of feeding by β_2-microglobulin, a marker of immune activation. Am J Physiol 1995;268:R1513
16. Plata-Salamán CR. Meal patterns in response to the intracerebroventricular administration of interleukin-1β in rats. Physiol Behav 1994;55:727

17. Plata-Salamán CR, ffrench-Mullen JMH. Intracerebroventricular administration of a specific IL-1 receptor antagonist blocks food and water intake suppression induced by interleukin-1β. Physiol Behav 1992;51:1277
18. Plata-Salamán CR, Borkoski JP. Interleukin-8 modulates feeding by direct action in the central nervous system. Am J Physiol 1993;265:R877
19. Plata-Salamán CR. Dexamethasone inhibits food intake suppression induced by low doses of interleukin-1β administered intracerebroventricularly. Brain Res Bull 1991;27:737
20. Yang Z-J, Koseki M, Meguid MM, et al. Synergistic effect of rhTNF-α and rhIL-1α in inducing anorexia in rats. Am J Physiol 1994;267:R1056
21. Lipton JM, Catania A. Pyrogenic and inflammatory actions of cytokines and their modulation by neuropeptides: Techniques and interpretations. Methods Neurosci 1993;17:61
22. Krueger JM, Kapás L, Kimura M, Opp MR. Somnogenic cytokines: Methods and overview. Methods Neurosci 1993;17:111
23. Rivest S, Rivier C. The role of corticotropin-releasing factor and interleukin-1 in the regulation of neurons controlling reproductive functions. Endocr Rev 1995;16:177
24. van Miert ASJPAM, Kaya F, van Duin CTM. Changes in food intake and forestomach motility of dwarf goats by recombinant bovine cytokines (IL-1β, IL-2) and IFN-γ. Physiol Behav 1992;52:859
25. Plata-Salamán CR. Interferons and central regulation of feeding. Am J Physiol 1992;263:R1222
26. Moldawer LL, Andersson C, Gelin J, et al. Regulation of food intake and hepatic protein synthesis by recombinant-derived cytokines. Am J Physiol 1988;254:G450
27. Roberts NJ Jr. Impact of temperature elevation on immunologic defenses. Rev Infect Dis 1991;13:462
28. Toth LA, Tolley EA, Krueger JM. Sleep as a prognostic indicator during infectious disease in rabbits. Proc Soc Exp Biol Med 1993;203:179
29. Boumpas DT, Paliogianni F, Anastassiou ED, et al. Glucocorticosteroid action on the immune system: molecular and cellular aspects. Clin Exp Rheumatol 1991;9:413
30. Plata-Salamán CR. Regulation of hunger and satiety in man. Dig Dis 1991;9:253
31. Chance WT, Fischer JE. Aphagic and adipsic effects of interleukin-1. Brain Res 1991;568:261
32. Plata-Salamán CR, Oomura Y, and Kai Y. Tumor necrosis factor and interleukin-1β: suppression of food intake by direct action in the central nervous system. Brain Res 1988;448:106
33. Hellerstein MK, Meydani SN, Meydani M, et al. Interleukin-1-induced anorexia in the rat. Influence of prostaglandins. J Clin Invest 1989;84:228
34. Shimomura Y, Inukai T, Kuwabara S, et al. Both cyclooxygenase and lipoxygenase inhibitor partially restore the anorexia by interleukin-1β. Life Sci 1992;51:1419
35. Uehara A, Ishikawa Y, Okumura T, et al. Indomethacin blocks the anorexic action of interleukin-1. Eur J Pharmacol 1989;170:257
36. Plata-Salamán CR. Strategies for potential manipulation of anorexia during acute and chronic disease. Nutrition 1995;11:702
37. Linthorst ACE, Flachskamm C, Muller-Preuss P, et al. Effect of bacterial endotoxin and interleukin-1β on hippocampal serotonergic neurotransmission, behavioral activity, and free corticosterone levels: An in vivo microdialysis study. J Neurosci 1995;15:2920
38. Shintani F, Kanba S, Nakaki T, et al. Interleukin-1β augments release of norepinephrine, dopamine, and serotonin in the rat anterior hypothalamus. J Neurosci 1993;13:3574
39. Montuschi P, Tringali G, Currò D, et al. Evidence that interleukin-1β and tumor necrosis factor inhibit gastric fundus motility via the 5-lipoxygenase pathway. Eur J Pharmacol 1994;252:253
40. Sütö G, Király Á, Taché Y. Interleukin-1β inhibits gastric emptying in rats: Mediation through prostaglandin and corticotropin-releasing factor. Gastroenterology 1994;106:1568
41. Saperas E, Yang H, Taché Y. Interleukin-1β acts at hypothalamic sites to inhibit gastric acid secretion in rats. Am J Physiol 1992;263:G414
42. Fargeas MJ, Fioramonti J, Bueno L. Central action of interleukin-1β on intestinal motility in rats: Mediation by two mechanisms. Gastroenterology 1993;104:377
43. Uehara A, Sekiya C, Takasugi Y, et al. Anorexia induced by interleukin 1: involvement of corticotropin-releasing factor. Am J Physiol 1989;257:R613
44. Daun JM, McCarthy DO. The role cholecystokinin in interleukin-1-induced anorexia. Physiol Behav 1993;54:237
45. Plata-Salamán CR. Immunoregulators in the nervous system. Neurosci Biobehav Rev 1991;15:185
46. Chance WT, Balasubramaniam A, Dayal R, et al. Hypothalamic concentration and release of neuropeptide Y into microdialysates is reduced in anorectic tumor-bearing rats. Life Sci. 1994;54:1869
47. Chance WT, Balasubramaniam A, Fischer JE. Neuropeptide Y and the development of cancer anorexia. Ann Surg 1995;221:579
48. Opara EI, Laviano A, Meguid MM, et al. Correlation between food intake and CSF IL-1 alpha in anorectic tumor bearing rats. NeuroReport 1995;6:750
49. Dinarello CA. The interleukin-1 family: 10 years of discovery. FASEB J 1994;8:1314
50. Plata-Salamán CR. Immunomodulators and feeding regulation: A humoral link between the immune and nervous systems. Brain Behav Immun 1989;3:193
51. Plata-Salamán CR, Borkoski JP. Chemokines/intercrines and central regulation of feeding. Am J Physiol 1994;266:R1711
52. Langhans W, Balkowski G, Savoldelli D. Differential feeding responses to bacterial lipopolysaccharide and muramyl dipeptide. Am J Physiol 1991;261:R659
53. Plata-Salamán CR, Borkoski JP. Centrally administered bacterial lipopolysaccharide depresses feeding in rats. Pharmacol Biochem Behav 1993;46:787
54. Van der Meer MJM, Sweep CGJF, Pesman GJ, et al. Synergism between IL-1β and TNF-α on the activity of the pituitary-adrenal axis and on food intake of rats. Am J Physiol 1995;268:E551
55. Langhans W, Savoldelli D, Weingarten S. Comparison of the feeding response to bacterial lipopolysaccharide and interleukin-1β. Physiol Behav 1993;53:643
56. Banks WA, Ortiz L, Plotkin SR, et al. Human interleukin (IL) 1α, murine IL-1α and murine IL-1β are transported from blood to brain in the mouse by a shared saturable mechanism. J Pharmacol Exp Ther 1991;259:988
57. Hickey WF, Hsu BL, Kimura H. T-lymphocyte entry into the central nervous system. J. Neurosci. Res. 1991;28:254
58. Goehler LE, Busch CR, Tartaglia N, et al. Blockade of cytokine induced conditioned taste aversion by subdiaphragmatic vagotomy: Further evidence for vagal mediation of immune-brain communication. Neurosci Lett 1995;185:163
59. Thomas WE. Brain macrophages: Evaluation of microglia and their functions. Brain Res Rev 1992;17:61
60. Giulian D, Corpuz M. Microglial secretion products and their impact on the nervous system. Series: Adv Neurol 1993;59:315
61. Aloisi F, Care A, Borsellino G, et al. Production of hemolymphopoietic cytokines (IL-6, IL-8, colony-stimulating factors) by normal human astrocytes in response to IL-1β and tumor necrosis factor-α. J Immunol 1992;149:2358
62. Breder CD, Dinarello CA, Saper CB. Interleukin-1 immunoreactive innervation of the human hypothalamus. Science 1988;240:321
63. Freidin M, Bennett MVL, Kessler JA. Cultured sympathetic neurons synthesize and release the cytokine interleukin 1β. Proc Natl Acad Sci USA 1992;89:10440
64. Molenaar GJ, Berkenbosch F, van Dam A-M, et al. Distribution of interleukin 1β immunoreactivity within the porcine hypothalamus. Brain Res 1993;608:169
65. Kuriyama K, Hori T, Mori T, et al. Actions of interferon-α and interleukin-1β on the glucose-responsive neurons in the ventromedial hypothalamus. Brain Res Bull 1990;24:803
66. Plata-Salamán CR, ffrench-Mullen JMH. Interleukin-1β inhibits calcium channel currents in isolated hippocampal CA1 neurons through protein kinase C. Eur J Pharmacol 1994;266:1
67. Weingarten S, Senn M, Langhans W. Does a learned taste aversion contribute to the anorectic effect of bacterial lipopolysaccharide? Physiol Behav 1993;54:961
68. Janz LJ, Brown R, Zuo L, et al. Conditioned taste aversion but not adrenal activity develops to ICV administration of interleukin-1 in rats. Physiol Behav 1991;49:691
69. Tazi A, Crestani F, Dantzer R. Aversive effects of centrally injected interleukin-1. Neurosci Res Commun 1990;7:159

70. Bauer C, Weingarten S, Senn M, et al. Limited importance of a learned aversion in the hypophagic effect of interleukin-1β. Physiol Behav 1995;57:1145
71. Fong Y, Moldawer LL, Marano M, et al. Cachectin/TNF or IL-1α induces cachexia with redistribution of body proteins. Am J Physiol 1989;256:R659
72. Gelin J, Andersson C, Lundholm K. Effects of indomethacin, cytokines, and cyclosporin-A on tumor growth and the subsequent development of cancer cachexia. Cancer Res 1991;51:880
73. Iseki H, Kajimura N, Ohue C, et al. Cytokine production in five tumor cell lines with activity to induce cancer cachexia syndrome in nude mice. Jpn J Cancer Res 1995;86:562
74. Strassmann G, Jacob CO, Evans R, et al. Mechanisms of experimental cancer cachexia. Interaction between mononuclear phagocytes and colon-26 carcinoma and its relevance to IL-6-mediated cancer cachexia. J Immunol 1992;148:3674
75. Fujimoto-Ouchi K, Tamura S, Mori K, et al. Establishment and characterization of cachexia-inducing and -non-inducing clones of murine colon 26 carcinoma. Int J Cancer 1995;61:522
76. Henderson JT, Seniuk NA, Richardson PM, et al. Systemic administration of ciliary neurotrophic factor induces cachexia in rodents. J Clin Invest 1994;93:2632
77. Fantuzzi G, Benigni F, Sironi M, et al. Ciliary neurotrophic factor (CNTF) induces serum amyloid A, hypoglycaemia and anorexia, and potentiates IL-1 induced corticosterone and IL-6 production in mice. Cytokine 1995;7:150
78. Ulenkate HJLM, Kaal ECA, Jennekens FGI. Ciliary neurotrophic factor induces hypophagia, hypodipsia, and diminished weight gain in young adult rats. Neurosci Res Commun 1995;16:67
79. Langstein HN, Doherty GM, Fraker DL, et al. The roles of γ-interferon and TNF α in an experimental rat model of cancer cachexia. Cancer Res 1991;51:2302
80. Matthys P, Dijkmans R, Proost P, et al. Severe cachexia in mice inoculated with interferon-γ-producing tumor cells. Int J Cancer 1991;49:77
81. Tracey KJ, Cerami A. Tumor necrosis factor in the malnutrition (cachexia) of infection and cancer. Am J Trop Med Hyg 1992;47(Suppl.):2
82. Pelleymounter MA, Cullen MJ, Wellman CL. Characteristics of BDNF-induced weight loss. Exp Neurol 1995;131:229
83. Cheng J, Turksen K, Yu Q-C, et al. Cachexia and graft-vs.-host-disease-type skin changes in keratin promoter-driven TNFα transgenic mice. Genes Dev 1992;6:1444
84. Keller U. Pathophysiology of cancer cachexia. Support. Care Cancer 1993;1:290
85. Oliff A, Defeo-Jones D, Boyer M et al. Tumours secreting human TNF/cachectin induce cachexia in mice. Cell 1987;50:555
86. Smith BK, Conn CA, Kluger MJ. Experimental cachexia: effects of MCA sarcoma in the Fischer rat. Am J Physiol 1994;265:R376
87. Mrosovsky N, Molony LA, Conn CA, et al. Anorexic effects of interleukin-1 in the rat. Am J Physiol 1989;257:R1315
88. Otterness IG, Seymour PA, Golden HW, et al. The effects of continuous administration of murine interleukin-1α in the rat. Physiol Behav 1988;43:797
89. Weingarten S, Savoldelli D, Langhans W. Enhancement or loss of the hypophagic effect of interleukin-1 upon chronic administration. Physiol Behav 1992;52:831
90. Mulligan HD, Mahony SM, Ross JA, et al. Weight loss in a murine cachexia model is not associated with the cytokines tumour necrosis factor-α or interleukin-6. Cancer Lett 1992;65:239
91. Mahony SM, Beck SA, Tisdale MJ. Comparison of weight loss induced by recombinant tumour necrosis factor with that produced by a cachexia-inducing tumour. Br J Cancer 1988;57:385
92. Shenouda G, Labateya M, Souhami L, et al. Elevated serum cytokines in patients with malignancy and weight loss. Int J Oncol 1993;2:115
93. Scagliotti GV, Gatti E, Ferrari G, et al. TNF-α determination in serum and pleural effusion in patients with lung cancer. Int J Oncol 1995;6:147
94. Aukrust P, Liabakk N-B, Muller F, et al. Serum levels of TNF-α and soluble TNF receptors in human immunodeficiency virus type 1 infection—Correlations to clinical, immunological, and virologic parameters. J Infect Dis 1994;169:420
95. Ciardi M, Sharief MK, Thompson EJ, et al. High cerebrospinal fluid and serum levels of TNF-α in asymptomatic HIV-1 seropositive individuals. Correlation with interleukin-2 and soluble IL-2 receptor. J Neurol Sci 1994;125:175
96. Weinroth SE, Parenti DM, Simon GL. Wasting syndrome in AIDS: Pathophysiologic mechanisms and therapeutic approaches. Infect Agents Dis 1995;4:76
97. Madson KL, Moore TL, Lawrence JM, et al. Cytokine levels in serum and synovial fluid of patients with juvenile rheumatoid arthritis. J Rheumatol 1994;21:2359
98. Green A, Dobias SB, Walters DJA, et al. Tumor necrosis factor increases the rate of lipolysis in primary cultures of adipocytes without altering levels of hormone sensitive lipase. Endocrinology 1994;134:2581
99. Nonogaki K, Fuller GM, Fuentes NL, et al. Interleukin-6 stimulates hepatic triglyceride secretion in rats. Endocrinology 1995;136:2143
100. Feingold KR, Marshall M, Gulli R, et al. Effect of endotoxin and cytokines on lipoprotein lipase activity in mice. Arterioscler Thromb 1994;14:1866
101. Grunfeld C, Feingold KR. Tumor necrosis factor, interleukin, and interferon induced changes in lipid metabolism as part of host defense. Proc Soc Exp Biol Med 1992;200:224
102. Hyltander A, Körner U, Lundholm KG. Evaluation of mechanisms behind elevated energy expenditure in cancer patients with solid tumours. Eur J Clin Invest 1993;23:46
103. Alexander HR, Norton JA. Pathophysiology of cancer cachexia. In: Doyle D, Hanks G, MacDonald N, eds. *Oxford textbook of palliative medicine*. Oxford: Oxford University Press, 1993:316
104. Cangiano C, Testa U, Muscaritoli M, et al. Cytokines, tryptophan and anorexia in cancer patients before and after surgical tumor ablation. Anticancer Res 1994;14:1451
105. McDevitt TM, Todorov PT, Beck SA, et al. Purification and characterization of a lipid-mobilizing factor associated with cachexia-inducing tumors in mice and humans. Cancer Res 1995;55:1458
106. Plata-Salamán CR. Tumor necrosis factor (TNF) production in response to lipids: Immunomodulatory activity with clinical applicability? Nutrition 1994;10:179
107. Cooper AL, Gibbons L, Horan MA, et al. Effect of dietary fish oil supplementation on fever and cytokine production in human volunteers. Clin Nutr 1993;12:321
108. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989;320:265
109. Meydani SN, Endres S, Woods MM, et al. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. J Nutr 1991;121:547
110. Kremer JM, Robinson DR. Studies of dietary supplementation with n-3 fatty acids in patients with rheumatoid arthritis. World Rev Nutr Diet 1991;66:367
111. Zurier RB. Fatty acids, inflammation and immune responses. Prostaglandins Leukotrienes Essent Fatty Acids 1993;48:57
112. Denzlinger C, Kless T, Sagebiel-Kohler S, et al. Modulation of the endogenous leukotriene production by fish oil and vitamin E. J Lipid Mediators Cell Signalling 1995;11:119
113. Kumar GS, Das UN. Effect of prostaglandins and their precursors on the proliferation of human lymphocytes and their secretion of tumor necrosis factor and various interleukins. Prostaglandins Leukotrienes Essent Fatty Acids 1994;50:331
114. Meydani SN. Modulation of cytokine production by dietary polyunsaturated fatty acids. Proc Soc Exp Biol Med 1992;200:189
115. Mulrooney HM, Grimble RF. Influence of butter and of corn, coconut and fish oils on the effects of recombinant human tumour necrosis factor-α in rats. Clin Sci 1993;84:105
116. Cooper AL, Rothwell NJ. Inhibition of the thermogenic and pyrogenic responses to interleukin-1β in the rat by dietary n-3 fatty acid supplementation. Prostaglandins Leukotrienes Essent Fatty Acids 1993;49:615
117. Dagnelie PC, Bell JD, Williams SCR, et al. Effect of fish oil on cancer cachexia and host liver metabolism in rats with prostate tumors. Lipids 1994;29:195
118. Tisdale M, Beck SA. Inhibition of tumor-induced lypolysis in vitro and cachexia and tumor growth in vivo by eicosapentaenoic acid. Biochem Pharmacol 1991;41:103

119. Ayala A, Chaudry IH. Dietary n-3 polyunsaturated fatty acid modulation of immune cell function before and after trauma. Nutrition 1995;11:1
120. Molvig J, Pociot F, Worsaae H, et al. Dietary supplementation with ω-3-polyunsaturated fatty acids decreases mononuclear cell proliferation and interleukin-1β content but not monokine secretion in healthy and insulin-dependent diabetic individuals. Scand J Immunol 1991;34:399
121. Oster MH, Enders SR, Samuels SJ, et al. Megestrol acetate in patients with AIDS and cachexia. Ann Intern Med 1994;121:400
122. VonRoenn, JH. Randomized trials of megestrol acetate for AIDS-associated anorexia and cachexia. Oncology 1994;51(Suppl. 1):19
123. Loprinzi CL, Michalak JC, Schaid DJ, et al. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. J Clin Oncol 1993;11:762
124. Graham KK, Mikolich DJ, Fisher AE, et al. Pharmacologic evaluation of megestrol acetate oral suspension in cachectic AIDS patients. J Acquired Immune Defic Syndr 1994;7:580
125. Neri B, Gemelli MT, Tarantini P, et al. The role of megestrol acetate in neoplastic anorexia and cachexia. Curr Ther Res 1995;56:183
126. Kornblith AB, Hollis DR, Zuckerman E, et al. Effect of megestrol acetate on quality of life in a dose-response trial in women with advanced breast cancer. J Clin Oncol 1993;11:2081
127. Leinung MC, Liporace R, Miller CH. Induction of adrenal suppression by megestrol acetate in patients with AIDS. Ann Intern Med 1995;122:843
128. Steer KA, Kurtz AB, Honour JW. Megestrol-induced Cushing's syndrome. Clin Endocrinol 1995;42:91
129. McCarthy HD, Crowder RE, Dryden S, et al. Megestrol acetate stimulates food and water intake in the rat: effects on regional hypothalamic neuropeptide Y concentrations. Eur J Pharmacol 1994;265:99
130. Costa A-MN, Spence KT, Plata-Salamán CR, et al. Megestrol acetate modulates the residual calcium channel current via the G-protein α_S-subunit in acutely isolated rat ventromedial hypothalamic neurones. J Physiol Lond 1995;487:291
131. Popiela T, Lucchi R, Giongo F. Methylprednisolone as palliative therapy for female terminal cancer patients. Eur J Cancer Clin Oncol 1989;25:1823
132. Robustelli Della Cuna G, Pellegrini A, Piazzi M. Effect of methylprednisolone sodium succinate on quality of life in pre-terminal cancer patients: a placebo controlled, multi-center study. Eur J Cancer Clin Oncol 1989;25:1817
133. Nelson KA, Walsh D, Sheehan FA. The cancer anorexia-cachexia syndrome. J Clin Oncol 1994;12:213
134. Bartlett DL, Charland S, Torosian MH. Growth hormone, insulin, and somatostatin therapy of cancer cachexia. Cancer 1994; 73:1499
135. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manag 1995;10:89
136. Samlaska CP, Winfield EA. Pentoxifylline. J Am Acad Dermatol 1994;30:603
137. Lissoni P, Ardizzoia A, Perego MS, et al. Inhibition of tumor necrosis factor-alpha secretion by pentoxifylline in advanced cancer patients with abnormally high blood levels of tumor necrosis factor-alpha. J Biol Regul Homeostatic Agents 1993;7:73
138. Dezube BJ, Lederman MM, Spritzler JG, et al. High-dose pentoxifylline in patients with AIDS: Inhibition of tumor necrosis factor production. J Infect Dis 1995;171:1628
139. Breuillé D, Farge MC, Rosé F, et al. Pentoxifylline decreases body weight loss and muscle protein wasting characteristics of sepsis. Am J Physiol 1993;265:E660
140. Landman D, Sarai A, Sathe S. Use of pentoxifylline therapy for patients with AIDS-related wasting: Pilot study. Clin Infect Dis 1994;18:97
141. Makonkawkeyonn S, Limson-Pobre RNR, Moreira AL, et al. Thalidomide inhibits the replication of human immunodeficiency virus type 1. Proc Natl Acad Sci USA 1993;90:5974
142. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the *obese* gene product on body weigh regulation in *ob/ob* mice. Science 1995;269:540.
143. Campfield LA, Smith FJ, Guisez Y, et al. Recombinant mouse OB protein: Evidence for a peripheral signal linking adiposity and central neural networks. Science 1995;269:546
144. Tartaglia LA, Dembski M, Weng X, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell 1995;83:1263
145. Plata-Salamán CR. Anorexia induced by activators of the signal transducer gp 130. NeuroReport 1996;7:in press.
146. Sonti G, Ilyin SE, Plata-Salamán CR. Neuropeptide Y blocks and reverses interleukin-1β-induced anorexia in rats. Peptides 1996;17:in press
147. Sonti G, Ilyin SE, Plata-Salamán CR. Anorexia induced by cytokine interactions at pathophysiological concentrations. Am J Physiol 1996:in press

NOTE ADDED IN PROOF:

The obese gene product, leptin, has been proposed to be an important regulatory signal for the control of feeding and body weight.[142,143] The leptin receptor[144] is most related to glycoprotein 130, a common signal transducer among receptors for members of the interleukin-6 subfamily (e.g., interleukin-6, ciliary neurotrophic factor and leukemia inhibitory factor) which induce anorexia[50,145] and have been proposed to participate in the induction and/or progression of cachexia.[73-78] This evidence suggests a potential mechanism that may be involved in the regulation of feeding during physiological as well as pathophysiological conditions. It remains to be determined whether glycoprotein 130 and related molecules may represent a link, or unified mechanism, or final common pathway associated with feeding control in health and disease.

Recent evidence on blockage and reversal of IL-1β-induced anorexia by neuropeptide Y[146] suggest the importance in studying cytokine-peptide interactions in the regulation of feeding behavior. Understanding these endogenous interactions may produce strategies with potential therapeutic implications for chronic diseases associated with the anorexia/cachexia syndrome. Cytokine-cytokine interactions are also relevant to anorexia. Estimated pathophysiological concentrations of cytokines (e.g., interleukin-1β, tumor necrosis factor-α and/or interleukin-8) in the cerebrospinal fluid act centrally and additively or synergistically to decrease feeding.[147] Feeding inhibition by cytokine interactions may participate in disease- and immunotherapy-associated anorexia. This interactive model of cytokine-induced anorexia is consistent with the multicytokine interaction that occurs during activation of the immune system.

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